THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES.

JANUARY, 1907.

ORIGINAL ARTICLES.

THE PRINCIPLES UNDERLYING THE SURGERY OF THE STOMACH AND ASSOCIATED VISCERA.[1]

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Clinical surgery as applied to the stomach has lacked an accurate physiological and pathological basis. Certain diseased conditions have been relieved successfully, but the reasons for the results have often not been satisfactorily explained. This is especially true in regard to function. In the past we have founded our knowledge largely upon the scientific study of the dead; but this kind of information is grievously open to error, inasmuch as secondary complications and terminal infections frequently obscure the initial lesion, so that from the postmortem evidence we are not always able to get a clear mental picture of the disease during the curable period. The immediate cause of death may be, apparently, disassociated from the primary lesion, which, although completely healed, had set in motion the fatal pathological process. As a foundation, medicine is greatly indebted to postmortem pathology, but as a superstructure, this has a less exalted position, and, too closely followed, leads to inefficiency and pessimism.

Modern surgery has dealt with the practical side and established a "living pathology." It has cleared up those three great avenues of peritoneal infection—the Fallopian tube, the appendix, and the gall-bladder—and is now engaged in a surgical investigation into the diseases of the stomach. The problems to be elucidated, however,

[1] The Mütter Lecture of the College of Physicians of Philadelphia, delivered December 4, 1906.

are very different from those just mentioned, since infections, primarily, play but a small part in gastric pathology. The gap between the knowledge obtained from postmortem study and the clinical findings must be bridged by animal experiments.

In the past we have depended too much upon form without inquiring sufficiently close into function. At present there is an extraordinary interest in physiological experimentation, and its effect upon surgery has been most beneficial. The work of Carrel, Crile, Cushing, and especially Cannon,[1] whose investigations in this field have added so largely to our real knowledge, are conspicuous examples of the trend of recent progress. A vast amount of work in the practical and comparative anatomy of the gastrointestinal tract, has been done by Cunningham, Huntington, McClellan, Deaver, and others, and in the experimental physiology of the digestive system by Pawlow, Starling, and a host of co-workers. It is with the view of bringing together and correlating some of the undigested facts in embryology, anatomy, physiology, and pathology, *which have a bearing on sound surgical practice*, that this paper is written.

I.

The study of the embryology of the gastrointestinal canal is most interesting and instructive and shows how much more permanent is function than form. The primitive intestinal tube is composed of three fundamental parts, the "foregut," the "midgut," and the "hindgut." In form the small intestine begins at the pylorus and the large intestine at the ileocecal valve; but functionally they maintain the rudimentary type, the small intestine beginning in the duodenum, just below the common duct, probably at the muscle described by Ochsner,[2] which he has shown is to be found near the juncture of the second and the third portions of the duodenum; and the large intestine begins near the splenic flexure of the colon (Kieth). The ancients, in calling the cecum a second stomach, were much nearer the truth than we have thought.

From the embryological foregut we get the back wall of the pharynx the œsophagus, the stomach, and the duodenum to its third portion, the liver and pancreas being developed from the duodenal end. The gall-bladder and common duct are direct invaginations of duodenal structures (Cunningham). It will be at once noted that all of these organs having their origin in the foregut have to do with the preparation of food for digestion, but are not, themselves, capable of absorption. The stomach and the duodenum have some selective action in absorbing certain things, such as stimulants. In operating upon the upper gastrointestinal tract soon after a

[1] Amer. Jour. Med. Sci., 1906, cxxxi, 563.
[2] Trans. Amer. Surg. Assoc., 1905.

meal, I have often been struck with the milky lines made by the full lacteals in the jejunum, while no such appearance was present above this point.

The duodenum with its wide caliber, fixed position, and its delivery point nearly as high as its pyloric origin, enables the chyme from the stomach to be thoroughly mixed with the pancreatic and biliary juices, absorption taking place below Ochsner's muscle. The jejunum and ileum take up the solid portions of the food, absorbing at least 90 per cent. of the proteids, but by no means do they dispose of all of the fluids. The contents of the ileum at the ileocecal valve are still in the liquid state, though the ingesta have lost the bulk of their nutritive elements. The cecum absorbs the fluids which are held for this purpose between the ileo-cecal apparatus and a physiological muscular contracture (the ceco-colic sphincter) near the hepatic flexure of the colon. In this intestinal segment, the contents are churned back and forth until the fluids have been re-absorbed, and the waste solids driven further along into the transverse colon. It is easily seen that the midgut retains its primitive characteristics; in the jejunum, ileum, cecum, and adjacent colon all of the absorption takes place. Man prepares his food with the organs which have their origin in the foregut, and absorbs his nutrition from the derivatives of the midgut, that is, he eats with the jejunum and the ileum and drinks with the cecum. The posterior "no-loop" gastrojejunostomy does not, therefore, deprive the patient of any appreciable amount of absorbing surface, and the nutrition is in every respect normal. The cecal function explains why cholecystenterostomy into the hepatic flexure of the colon has proved so successful an alleviation in complete obstruction of the common bile duct, when the duodenum for any reason could not be used for the purpose. The continuous bile flow seems to prevent an ascending infection from the colon, although, as compared with the duodenum, it contains quantities of highly virulent organisms. When a permanent external cholecystostomy is made the patient loses with the bile-discharge twenty to thirty ounces of fluid each day, thereby being compelled to drink a larger quantity of liquid, and at best shows signs of dehydration; whereas, when the bile fluids are turned into the cecum they are quickly reabsorbed. The effect of the bile in digestion, especially in aiding the pancreatic ferments, is of course lost, but its usefulness upon the function of the large intestine is preserved.

The value of water in the human economy is testified to by the fact that it is re-distilled in the cecum, and used in the system over and over again. The mechanical effects of fluids in carrying solids as far as the cecum cannot be over-estimated, but beyond this situation liquids would interfere with the storage function.

The primitive hindgut begins near the splenic flexure of the colon, and although largely a matter of convenience, this portion

of the intestine has a very considerable nutritive function. The normal action of the upper colon is antiperistaltic, except during defecation. Mr. Bond, in his most admirable address on surgery[1] before the British Medical Association in 1905, showed that particles of indigo-carmine placed inside the anus are carried upward by what he calls "reverse mucous currents." This process occurs close to the intestinal mucous membrane and takes place in spite of bowel passages.

Cannon in his experiments also finds that antiperistalsis is the normal movement in the upper large intestine. By selective action valuable food elements, and especially fluids, are carried back into the cecum. Great advantage has been taken of this physiological fact by the giving of saline infusions by the rectum. Murphy has shown that salines introduced very slowly into the rectum will be absorbed with great rapidity, largely by reverse peristalsis to the cecum. From two to four quarts, which otherwise could not be introduced into the body, except by hypodermoclysis or venous transfusion, can be taken up in this manner. Especially valuable is this in connection with gastric surgery when the stomach is not available and fluids are essential.

Comparative physiology is interesting as showing that in carnivorous animals digestion is practically completed in the small intestine, while in herbivorous animals the colon is equally important, on account of the liquid nature of the plant and grass juices upon which they depend for nourishment. The human species occupies an intermediate position.

II.

The dome of the stomach follows the curve of the diaphragm and rises above the œsophageal opening. In searching with the hand in the stomach for the cardiac orifice, one unconsciously tends to pass above the actual situation, especially as, on irritation, the cardia contracts, leaving the mucous membrane nearly smooth. A little dimple, however, can be found, and steady pressure at this point for a short time, allows the finger to pass through the opening. The lesser curvature has a somewhat fixed position, in the anesthetized patient about two-thirds of its extent hanging nearly longitudinal with the long axis of the body, while the lower, horizontal third, turns sharply to the right and somewhat upward, varying from two to three and a half inches in length. Distention of the stomach comes about, almost entirely, through alterations in the relations of the greater curvature.

The stomach is a contractile organ, exercising its functions through muscular action, gravity playing but a small part in the onward

[1] Brit. Med. Jour., 1905, ii, 232.

progress of food. When distended it extends downward and to the right, the pylorus being carried across the median line and upward to prevent the weight of the food resting against the pyloric sphincter. In all distended organs having storage function, this elevation of the outlet will be found to prevent continuous exertion of muscular force for retention purposes, as is shown in the urinary and gall-bladders. The stomach is emptied of its contents not only by general contraction, but also through muscular bands which extend downward from the fundus, grasping the greater curvature (Cannon). As these bands contract the greater curvature is shortened and the pyloric outlet brought more nearly to the bottom of the cavity.

In a general way it can be said that all of the stomach lying to the left of the longitudinal part of the lesser curvature has storage function (fundus), about four-fifths of the whole (Starling). On the right, having the horizontal part of the lesser curvature as its superior wall, is the antrum, the grinding portion of the stomach. There is said to be a slight thickening of the circular muscular fibers at the entrance to this cavity. Starling states that this is apparent rather than real, and that the antrum is a physiological, and not an anatomical, compartment. By contraction of these circular muscle fibers the food masses are powerfully held in the pyloric end during the kneading process; some prepared chyme escapes through the pylorus, while a much larger amount of food is ejected backward into the fundus which steadily compresses the whole. In pyloric obstruction the antrum loses its identity and becomes a part of the distended fundus, as in the cadaver, accounting for the perfect drainage of a gastrojejunostomy, whereas, if the same operation is done and the pylorus be unobstructed, the artificial stoma fails to drain and is often productive of harm, since the muscular action of the stomach propels the food out through the normal outlet, without regard to the gastroenterostomy.

The terminal three-fourths inch of the stomach next to the pylorus can be classed with the pyloric apparatus, since it has but comparatively little to do with the food grinding, and acts rather as a funnel with the apex at the pyloric ring (the pyloric canal of Jonnesco). The pylorus, under the muscular contractions of the stomach, projects into the duodenum and, from the duodenal side, greatly resembles the vaginal portion of the cervix.

The importance of these muscular features is shown by the fact that nearly 80 per cent. of all ulcers of the stomach are situated in this grinding, pyloric end, the most common variety being the saddle ulcer of the lesser curvature, extending flap-like down the anterior and posterior surfaces (pre-pyloric). The ulcer crater, if one be present, will usually be found upon the posterior wall, or there will be two ulcers facing each other, one anterior and the other posterior, connected superiorly by a bridge of induration.

The pylorus is seldom primarily involved in ulceration, since the pyloric canal is normally contracted, and is less exposed to mechanical injury, or the presence of an excess of acid secretions. The large majority of so-called pyloric ulcers are in reality duodenal. The duodenal ulcer extends up to the pylorus, or within three-fourths inch of it, in 96 per cent. of all the cases; error in accurate localization has led to mistaken identification. As a matter of fact, we find at the operating table that no less than 40 per cent. of all gastric and duodenal ulcers are situated in the duodenum.

On the peritoneal surface of the gastric side of the pyloric ring will be found a peculiar arrangement of the bloodvessels which is rather constant. From the lower side a thick vein passes upward somewhat more than half-way upon the anterior surface. From the upper border a second vein reaches downward in the same line, nearly, if not quite, meeting the first.

Not only is ulceration most frequent in the antrum, but the topography of gastric cancer will be found to be the same as ulcer. In 54 per cent. of 134 resections of the stomach we found malignant disease originating in the submucous tissue at the margin of an ulcer. Primary cancer of the duodenum, however, is rare. We have seen only two instances, although four times we have found carcinoma developing on the gastric side of a duodenal ulcer which had involved the pylorus.

The pyloric antrum occupies a sheltered position under the left lobe of the liver, and this is also true of the duodenum above the common duct. As contrasted with the remainder of the stomach, acute ulcer perforations into the free peritoneal cavity are relatively uncommon in the antrum on account of the ease with which adhesions to the liver, gastrohepatic omentum, the suspensory ligament, and the gall-bladder are formed, and these tend to prevent the gastric contents from escaping. The cardiac end of the stomach has no such protection, and although this region has but 10 per cent. of the total number of ulcers, acute unprotected perforations are here more frequent than in the entire antrum. Perforations of duodenal ulcers are more common than gastric, but the sheltered situation of the duodenum enables ready adhesive protection, while its contents are nearly sterile, and relatively small in amount.

The bloodvessels supplying the stomach are derived from the cœliac axis and are four in number: the gastric, which reaches the stomach on the lesser curvature just below the œsophageal opening; the superior pyloric branch of the hepatic artery at the pylorus; the gastroduodenal, which gives rise to the right gastroepiploic; and the left gastroepiploic, from the splenic artery.

The bloodvessels of the lesser curvature lie in the wall of the stomach; those of the greater curvature are to be found at considerable distance from the gastric wall, arterial branches passing upward from the gastroepiploics upon the stomach, anteriorly and pos-

teriorly in a saw-buck manner. When the stomach is distended, this permits the greater curvature to sag downward toward the bloodvessels without compressing them, enabling rapid change in size and position.

Tortuosity of the uterine arteries makes possible the great size of the uterus during pregnancy, because it comes on slowly, but tortuosity would not allow the rapid changes to which the vessels of the greater curvature of the stomach are subjected. By tying the four bloodvessels, gastrectomy can be made bloodless, just as hysterectomy is in the modern operation.

The lymphatic arrangement is nearly the same as the vascular, but varies in one important particular. On the greater curvature no lymph nodes are to be found to the left of its middle, and the lymphatic circulation of this region is from left to right (Cuneo). Therefore, in radical operations for cancer, it is possible to save a great deal of the greater curvature. On the contrary, in the lesser curvature the lymphatic structures lie in the submucous tissues, rendering it necessary in every case of carcinoma of the pyloric end to remove all of the lesser curvature as high as the gastric artery (Mikulicz). The glands about the pylorus are most numerous on the inferior surface, although several are found just above it in the line of the pyloric artery. The relation of these glands to the field of gastric cancer was long ago dwelt upon by Kocher. The dome, arising above and to the left of the cardiac orifice, is disconnected from the remainder of the stomach in its blood supply and lymphatic supply (Robson and Moynihan). The lymphatics of the stomach, in a general way, greatly resemble those of the other hollow viscera; the neck of organs is the region of the lymphatics, the fundus being less well supplied.

III.

Thanks to the investigations of a large number of experimental physiologists, we know many of the secrets connected with the functions of the stomach and duodenum. One important fact developed is that the stomach not only has many ferments, but that these are called into action by the character of the ingesta, and that they can be increased or diminished by appropriate diet.

Gastric function is carried on to a considerable extent independently of the nerve supply. The chyme when ready to leave the stomach has attained a proper acidity, which causes contraction of the gastric muscles, and the pylorus opens automatically to permit the escape of the chyme. The duodenum also has control over the pylorus, and acidity is here again a feature influencing the pyloric closure. According to Kelling, the chemistry of the duodenal contents is the most important agent in the control of the

pylorus. The mucous membrane of the antrum produces specific substances called hormones (Starling), which, acting with nerve impulses, such as sight, taste, and smell, control the amount of food ingested and the necessary gastric secretion.

Not only is much of this process the result of chemistry, but the same force, through the vascular system, stimulates the glandular activity of the liver and pancreas. It has been shown that the introduction of chyme into the duodenum causes pancreatic secretion by means of a product of the intestinal mucous membrane called "secretin," when the pancreas has no connection with the body excepting its blood supply. The great protective agent in preventing self-digestion in the stomach is mucous, and this is apparently true of the entire gastrointestinal canal.

The stomach equalizes the temperature of the ingesta, macerates the food masses in a weak solution of hydrochloric acid and pepsin, and converts the contents into a harmonious whole, the muscular action of the pyloric antrum being the active agent in the latter process. The cardiac end is a temporary storehouse, which enables its possessor to place rapidly a quantity of material where it can be drawn upon as digestion proceeds. To a large extent, then, the stomach is a convenience and obviates the necessity of continuous feeding, just as the urinary bladder and the large intestine beyond the splenic flexure are conveniences to prevent continuous elimination.

Excess or changed secretions, especially acidity, seem to lie behind much of the pathology of the stomach, accounting largely for ulcer in the pyloric antrum and duodenum above the common duct, with its alkaline secretions. Trauma plays an important part in the production of ulcer. We have but to remember the frequency of this malady in the grinding pyloric end of the stomach, and to note that duodenal ulcer usually *originates at the point* which receives the impact of the chyme *forcibly ejected* from the pylorus, to appreciate the influence of local injury in gastric disease.

It has been supposed that gastrojejunostomy would pass the food too quickly from the stomach into the intestine. This fear, however, has been proved groundless, since the stomach does not contract in such a manner as to discharge its contents until the proper chemical conditions have been reached, and the food is ground in the antrum before propulsion is begun.

It is altogether probable that modern methods of food preparation have greatly changed gastric digestion, and that a considerable share of the now very prevalent diseases of the stomach is due to modern dietary changes from primitive conditions, just as the loss of necessity for the grinding action of the teeth has resulted in their premature decay. In aboriginal races many diseases of civilization, such as appendicitis, gallstones, ulcer, and cancer, seem to be rare (Senn).

The nerve supply of the stomach is of two kinds, the vagus and the sympathetic. During fetal rotation, the stomach turns upon its right side, which thereby becomes the posterior wall, and the left vagus lies anteriorly. Terminal filaments of the vagi join with the sympathetic fibers from the abdominal ganglion and form the plexuses of Auerbach and Meissner, which lie in the gastrointestinal wall.

The control of the cerebrospinal nerves over the stomach is limited and has to do with food requirements, but, as far as actual digestion is concerned, the sympathetic is the controlling factor. Beyond the stomach the cerebrospinal system is even less influential, until the sigmoid and the rectum are reached, where again conscious control is essential.

The sympathetic nervous system, developed from mesoblastic tissue, is undoubtedly the primitive one. It is closely allied with the control that is inherent in the gastro-intestinal muscles, and which is myogenic in origin, and of the same nature as His' heart muscle band which regulates the heart-beat. The action of the gastrointestinal canal is regulated largely by this mysterious myogenic force.

The sympathetic nervous system has retained, to a large extent, its primitive control over those organs which have to do with the maintenance of the body, but it is altogether probable that it is losing its prominence on account of the overshadowing development of the cerebrospinal system, and, just as other vestiginal organs, like the gall-bladder, appendix, and wisdom teeth, seem to develop a tendency to disease, so possibly does this mysterious nerve body. It is within the realms of possibility that abdominal ptosis and many forms of neurasthenia are characteristic expressions of evolutionary instability of the sympathetic nervous system.

The one essential difference between the sympathetic and the cerebrospinal system is that the sympathetic is not segmented, and is, therefore, unable to prevent general disturbances upon irritation of any of its component parts. This is especially interesting in connection with certain diseases of the stomach which are exceedingly misleading and which apparently have a common origin, such as pyloric spasm, atonic dilatation, prolapse of the stomach, and gastric neuroses. Now that surgery of the stomach is occupying such an important place, it is vital that we should eliminate these conditions from the operating-room.

We have had a surgical opportunity in a considerable number of cases to examine the stomach during that contraction of the pyloric canal and antrum which constitutes "pyloric spasm." This muscular contraction, when present, causes the patient to experience a sensation which he speaks of as gas pain. It can be observed in operative examination under local anesthesia. The peculiar appearance of the stomach during pyloric spasm may give rise to the belief that physical disease exists, because of a roughened, puckered

appearance, which lasts a fraction of a minute, and then changes position or develops a rhythmic contraction, confined to the antrum.

In the most extreme degrees we have found it in connection with stones in the appendix, impacted gallstones, tuberculosis of the intestine, and chronic intestinal obstructions of various kinds. Clinically, it would appear that irritation of any part of the gastrointestinal canal and allied organs, the liver and pancreas, may produce pyloric spasm, and that this condition may overshadow the local disease. Cannon in his experimental work found that after severe injury to the intestinal wall the pylorus became closed and remained so for several hours. It would appear that control of the pyloric sphincter is vested not only in the stomach and duodenum, but also in all of the derivatives of the midgut, including the cecum, and that pyloric spasm may and often does originate in the attempt to prevent food entering the irritated intestinal tract, or, in some instances, a perversion of the physiological function. The greatest care is necessary in differentiating these cases from gastric ulcer and other inflammatory infections.

While it is possible that pyloric spasm may exist as the result of a mucous ulcer, as believed by Eiselberg and Doyen, such is not our conviction, although spasm will mimic gastric ulcer clinically and is often diagnosticated as such. We are inclined to look with a great deal of suspicion upon any supposed ulcer of the stomach which cannot be absolutely demonstrated, not only to the operator, but to onlookers as well.

IV.

The contents of the fasting stomach are relatively sterile; this is equally true at the height of digestion, the chyme, when discharged into the duodenum, being nearly free from pathogenic organisms. This is due largely to the acid gastric secretion; while not actively germicidal, the general influence of all of the secretions of the stomach are against germ life. Cooking renders a large amount of the food consumed sterile, but during mastication many organisms are picked up from the mouth, which teems with bacteria of all kinds (Harrington). Cushing found that with sterilized food the discharge from a jejunal fistula was full of micro-organisms (providing the mouth was kept in good condition), and recommended, in addition to sterilizing the food, antiseptic oral washes and careful cleansing of the teeth previous to operations upon the gastrointestinal tract. The vigorous use of the tooth-brush to those who are not accustomed to it may start up a gingivitis at the end of a few days and temporarily increase the virulence of the organisms. Such oral antisepsis in this class of patients should begin at least two weeks prior to the operation. As the average patient cannot be

kept in preparation such a length of time the practical importance of this step in the individuals just referred to is not great. A moderate number of bacteria, particularly bacilli, pass with the food into the duodenum and members of the colon group work upward from below.

Adami and Ford have shown that leukocytes pass out upon the free mucous surface of the duodenum and upper jejunum, picking up particles of fat and micro-organisms of various kinds, particularly bacilli, and by phagocytosis destroy them in the neighboring lymphatics. Some bacteria, however, are continuously carried to the liver and are there annihilated, the pigments of the slaughtered organisms giving rise to the little pigmented areas sometimes found in the liver. A varying number of bacteria, however, are passed through the liver and excreted with the biliary secretion. The bile, therefore, must be looked upon as always infected and it is probably this attenuated infection which gives rise to gallstone disease (Lartigau).

The relative sterility of the stomach and duodenum and the upper jejunum shows why gunshot wounds of this locality have been so much more often followed by recovery when operated upon than those farther down in the intestinal tract.

One interesting feature in this connection concerns the reason why gallstone disease is so much more frequent in women than men. In 1700 of these patients upon whom my brother and I have operated, three-fourths have been women, while just the opposite has been true of duodenal ulcer. In 209 operated cases of the latter disease 73 per cent. were males, and only 27 per cent. females. Granting that biliary infection is equal in men and women, is this sex disproportion due to different mechanical conditions? We have been investigating during life a considerable number of patients with a view to determining whether there is a difference in the arrangement of the duodenum and the common duct, which favored ascending gall-bladder infection in women, and, also, as to whether the mechanics in men were unfavorable for permitting the alkaline discharge from the common duct quickly to neutralize that excessive acidity of the chyme which seems to lie behind the etiology of duodenal ulcer. We have not been able to satisfy ourselves that there is sufficient anatomical difference to explain the phenomena. In the living male subject the first four inches of the duodenum has a higher upward curve than in the female, in whom the corresponding portion is more nearly horizontal—which may have some bearing on the question. There is no question that bacteria can, under certain circumstances, travel up the common duct into the gall-bladder. Bond found that indigo-carmine placed within the anus could be detected in the gall-bladder in about forty-eight hours. It is probable that this sex difference in gallstone disease is physiological, rather than anatomical, and possibly due in some way to the potential capacity of the female liver to care for mother and child.

As one passes down the intestinal canal, bacteria increase in numbers and in virulence, and, in the large intestine, bacterial growth adds considerably to the bulk of the stool. The acid change which takes place in the large intestine is probably caused by germ life rather than intestinal secretions, since the large intestine, when entirely free from feces, has, like the small intestine, an alkaline reaction (Bond).

The problem of securing asepsis during operations upon the upper abdomen is most interesting. To one who reads about the gastric surgery of five and ten years ago, the frequency of fatal results from pneumonia following operations upon the stomach is most noticeable; it had various explanations, the anesthetic and the aspiration of gastric contents regurgitated into the œsophagus, being the most generally accepted hypothesis. In Mikulicz's clinic it was brought out that part of the venous blood from the stomach, instead of passing through the portal vein so that the liver might sterilize it, returned directly through the vascular anastomoses about the cardiac orifice and that this unsterilized blood was the cause of a pneumonia which was embolic in character.

Muscatello demonstrated that the endothelial serous lining of the diaphragmatic area is exceedingly active in absorption, and, based upon this, Clark elevated the foot of the bed after abdominal operations to insure rapid absorption of septic products and prevent peritonitis. The unshed blood in the vessels has no germicidal properties and this septic material when absorbed before being acted upon by the proper tissues sometimes caused general sepsis or was carried to the lungs, producing embolic pneumonia of the same variety that had been noted after operations on the stomach. Fowler pointed out that the inherited resistance to peritonitis in the pelvis, which had been brought about by tubal diseases in women and appendicitis in both sexes, caused absorption in this locality to be slow and therefore advised that, in peritoneal sepsis, the head of the patient's bed should be raised and a drainage tube introduced into the pelvis to drain away the discharges. In connection with general septic peritonitis, we followed the Fowler method, excepting that we raised the patient's head and chest much higher. The betterment in the mortality in peritonitis, actual or impending, was remarkable, although it was soon noticed that, although the patient did very well, there was often no drainage from the tube, therefore drainage was not the sole factor. With the introduction of the holding-clamps during gastric operations, which help so much to prevent accidental soiling, and the raising of the patient to the semi-sitting posture, for a few days subsequently, lung complications have nearly disappeared.

In work upon the upper abdomen on the left side any fluids at once gravitate toward the diaphragm; on the right, they are pre-

vented from doing so by the liver. To prevent rapid absorption of these unsterilized products, the raising of the diaphragmatic area, so as to drain this material into the pelvis, is of the first importance, as here by means of the omentum and pelvic colon any septic particles can be rendered harmless by absorption through the lymphatics and radicals of the portal vein. So far as these organs which lie within the active radius of the portal vein are concerned, the liver must be looked upon as an adjuvant to the lymphatic glands in the destruction of micro-organisms.

The omentum, according to Dickinson, Buxton, and Torrey, is a most important agent in developing phagocytosis and opsonins, its germinating endothelium is constantly producing lymphocytes and is capable under proper stimulation of throwing both newly formed phagocytes and those called from a distance into germicidal action. This wiping process is greatly aided by the vermicular and swaying movements of the intestines, which, in spite of gravity, bring all parts of the small intestinal wall in contact with the omentum, the epiploic tags having the same function for the more fixed large intestine.

Dudgeon and Sargent have shown that from some source Staphylococcus albus first appears in peritoneal sepsis and rapidly produces a mild infection; this furnishes the necessary stimulus to the protective endothelium, so that the phagocytes are attracted in time to destroy the more virulent, but later developed, bacteria. Bond has demonstrated that the plastic exudate produced by Staphylococcus albus protects the weakened endothelium and prevents the micro-organisms passing directly into the blood stream. When absorbed by sound endothelium, bacteria are carried into the lymphatics and destroyed.

In closing let me quote from Dr. W. H. Welch's recent address on the occasion of the dedication of the new buildings of the Harvard Medical School: "There is a highly significant and hopeful scientific movement in internal medicine and surgery today, characterized by the establishment of laboratories for clinical research, by the application of refined physical, chemical, and biological methods to the problems of diagnosis and therapy, and by the scientific investigations along broad lines of the special problems furnished by the living patient."

THE PARAVERTEBRAL TRIANGLE OF DULNESS IN PLEURAL EFFUSION (GROCCO'S SIGN).

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In March, 1902, Grocco,[1] of Florence, described, in the following words, a new physical sign which he had observed in pleural effusions: "*Paravertebral triangle of the side opposite that of the pleural effusion.* When, with a pleural effusion of sufficient size, one percusses from above downward, along the spinous processes of the vertebræ, with the patient in the sitting posture, there appears, at the level of the fluid, a dulness which, relative at first, becomes absolute as one passes downward, in association with a progressively increasing sense of resistance. In like manner, by percussing downward on the healthy side, along lines parallel to the spinous processes, there is noted, opposite the dulness in the median line, a paravertebral area of deficient resonance, of triangular shape. One side of this dull area is represented by the line of the spinous processes; another, by the lower border of the area of thoracic resonance for a short distance which varies in length from two to three or more centimeters; the outer side is represented by a line which, starting from the base, rises obliquely to unite at an acute angle with the median line at about the upper limit of dulness. In a right-sided effusion, other things being equal, the paravertebral triangle has seemed to me more marked. Although symptomatology abounds in methods for differential diagnosis between pleural effusion and pulmonary infiltration, there can be no doubt that the sign which I have mentioned may be of value in some cases, especially in right-sided and encapsulated exudates. I shall return to this subject later with a detailed description which may illustrate that which, if I be not mistaken, is a diagnostic sign of pleural effusions hitherto undescribed and worthy of consideration."

Later in the same year, Grocco[2] exhibited two radiograms, one from a living patient, and one from a cadaver in which the chest had been filled with a solution of acetate of lead, demonstrating the fact that the shadow extended past the median line to an extent sufficient to account for the symptoms observed. Koryani,[3] in a study of

[1] Brevi note di semeiotica fisica. Riv. crit. di clin. med., Firenze, 1902, iii, 274–280.

[2] Triangolo paravertebrale opposto nella pleurite essudativa. Lavori di Cong. di med. int. (1902), Roma, 1903, 190.

[3] Ein Beitrag zur differentialen Diagnostik pleuritischen Ergüsse. Wien. klin. Rundschau, 1902, xvi, 300.

auscultatory percussion published shortly after Grocco's communication, noted that dulness in pleural effusions crosses the median line, extending over to the healthy side in such a manner as to agree essentially with the descriptions of Grocco. Following this, various clinical observers have given testimony to the diagnostic value of this sign: Silvestrini,[4] Maragliano,[5] Flora,[6] Pieraccini,[7] Bucco,[8] Berghinz,[9] Ferranini,[10] Baduel and Siciliano,[11] Cecchini,[12] Raucfuss,[13] Kozlovsky,[14] Kisel,[15] Kernig,[16] Gracheff,[17] Plessi,[18] and Ewart.[19] Barbieri,[20] on the other hand, on the basis of two cases in which he was unable to demonstrate the sign, and of several experiments on the cadaver in which he was unable, by intrapleural injections, to bring about marked displacement of the mediastinum, concludes that the sign can have no relation to the conditions on the diseased side. Ghelfi[21] also considers the sign uncertain and of obscure origin; he observed it in six cases only, out of thirteen. Rodrigues Alves[22] concludes that the sign is of no value, as modifications in the percussion sound of any sort in one-half of the back may cause a certain amount of change of the same character on the healthy side, in a strip along the spine which he considers somewhat analogous to the paravertebral triangle. This

[4] Discussion of Grocco's communication. Lavori di Cong. di med. int. (1902), Roma, 1903, 190.

[5] Contributo alla semeiotica dei versamentipleurici. Boll. d. soc. Eustach., Camerino, 1903, i, 18–27; Alcune forme di pleurite. Cron. d. clin. med. di Genova, 1903, ix, 145–149.

[6] Recenti noti semeiologiche sulle pleuriti. Riv. crit. d. clin. med., Firenze, 1902, iii, 407.

[7] Le polmonite massiva o pneumo-bronchite fibrinosa. Clin. mod., Pisa., 1903, ix, 5–8; Il suono retrosternale di Banti, ed il triangolo paravertebrale di Grocco. Clin. mod., Pisa, 1903, ix, 303–307.

[8] Il sintoma di Grocco: il triangolo paravertebrale opposto nella pleurite essudativa. Cronica della clin. med. del Prof. De Renzi in Napoli., N. Riv. clin. terap., Napoli, 1903, vi, 342.

[9] Sul triangolo paravertebrale di Grocco. Riv. crit. di clin. med., Firenze, 1904, v, 530.

[10] Il triangolo paravertebrale opposto di Grocco nei versament ipleurici unilateral ilibri. Riforma, Palermo-Napoli, 1904, xx, 953–955.

[11] Il traingolo paravertebrale di Grocco. Riv. crit. di clin. med., Firenze, 1904, v, 5;21; 37.

[12] Contributo allo studio del sintoma di Grocco, con speciale riguardo alla pleuriti sierosa o siero-fibrinosa destra. Riv. crit. di clin.-med., Firenze, 1904, v, 765–770.

[13] On paradoxical phenomena in percussion of the chest. Russky Vrach, S. Peterb., 1904, iii, 295–6; Die paravertebrale Dämpfung auf der gesunden Brustseite bei Pleuraergüssen Verhandl. d. Versamml. d. Gesellsch. f. Kinderk. Deutsch. Natur u. Aerste, 1904, Wiesb., 1905, xvi, 202–211, 1 pl. We have been unable to consult the original of this publication.

[14] Discussion of Rauchfuss' communication. Russky Vrach, 1904, iii, 296.

[15] Ibid.

[16] Ibid.

[17] Paravertebral dulness in pleuritic effusions and percussion of the spine. Kazan med. J., 1903, v, 39–51.

[18] Sul triangolo paravertebrale opposto di Grocco. Riv. crit. di. clin. med., Firenze, 1905, vi, 411–414.

[19] The practical value of Grocco's paravertebral triangle. Lancet, 1905, ii, 216; A rapid method for the diagnosis and estimation of pleural effusion. Polyclin., Lond., 1906, x, 13–16.

[20] Sul triangolo paravertebrale: Rendic. d. Ass. med. chir. di Parma, Roma, 1903, iv, 60.

[21] Sul triangolo paravertebrale di Grocco (contributo clinico). Parma, 1904, A. Bartoli, 16 p. 80.

[22] Do triangolo de Grocco, seu valor. semeiologico e sua semeiogenesis. Rio. de Jan., 1905, R. Braga. 79 p., 16 pl., 40.

he finds especially true in pneumonia. His plates, however, seem to indicate that he has failed to grasp the essential character of this sign. Gracheff finds paravertebral dulness on the healthy side a constant and valuable diagnostic sign. In some instances, however, he finds that the area is not triangular, but of a hemiovoid shape, the transverse measurement being greatest toward the upper part. He insists, especially, as does Signorelli,[23] on the importance of percussion of the spine. The paravertebral dulness, he thinks, may be simulated at times by changes at the base of the lung on the opposite side, particularly in pneumonia, but *flatness over the spine is distinctive of effusion.*

Rauchfuss, who maintains that he has been familiar with the sign for over twenty years, regards it as pathognomonic, although he admits that in some massive pneumonias he has noticed a slight, though rather indefinite dulness on the opposite side of the spine. In the several cases, however, in which such an observation was made there was no necropsy to prove the absence of fluid. Koslovsky, who recognizes the diagnostic value of the paravertebral triangle, has also seen a slight indefinite dulness on the side opposite a pneumonia. Rauchfuss observes that the hypothenuse of the triangle has sometimes a slight outward convexity.

Pieraccini, in a case of pneumothorax with a very small amount of fluid, noticed a clearer tympanitic note on the healthy side in an area analogous to that of the paravertebral triangle of dulness in pleural effusions.

Cecchini noted that, with small effusions, the area of dulness varied greatly according to whether the patient lay on the side affected, when the triangle almost disappeared, or sat up, when it became more marked. With large effusions, the variations with changes of position were slight. Plessi studied the auscultatory signs in the paravertebral triangle and observed that there is usually a marked diminution in the intensity of the respiratory murmur, becoming more evident as one approaches the spine. In one case he found that the characteristic tubular respiration heard over the effusion passed the spine, extending about to the external border of the area, so that it was possible to make out the triangle by auscultation. He also asserts that the coin sound, transmitted characteristically through a pleural effusion as a clear, metallic ring, is also heard in the same manner throughout the triangular area, as well as bronchophony and egophony. Finally, he observed that toward the outer part of the triangle, crepitant or fine moist rales were often heard, evidence, probably, of compressed lung.

With regard to the *cause* of the phenomenon, the studies of Baduel and Siciliano are especially important. Endeavoring to reproduce, experimentally, the conditions existing during life, they

[23] Di un nuovo metodo d' indagine diagnostica; la percussione della colonna vertebrale. Policlin., Roma, 1902–3, ix, sez. prat., 1345–1348.

filled the abdominal cavity with gelatin in such a manner as to support the diaphragm in its normal position. They then injected the vessels through the carotid. After this, fluid was introduced slowly into the pleural cavity while the subject was in a sitting posture. By this procedure a characteristic paravertebral triangle was produced. On opening the chest on the opposite side they were able to confirm the existence of increased pressure, as the lung tended to protrude from the wound as a hernia, while the finger could readily detect the displacement of the contents of the mediastinum—aorta, azygos vein, œsophagus, heart. In other cases, injecting the pleural cavity with gelatin and filling the gastro-intestinal tract with 10 per cent. formalin, they removed the extrem-

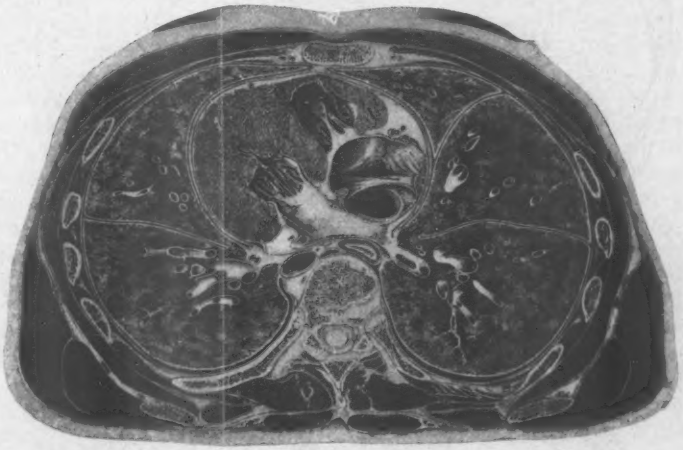

FIG. 1.—Transverse section at the level of the nipples. (From Braune's Atlas of Topographical Anatomy.)

ities and the skin, and, after making numerous incisions to allow the entrance of the fluid into the tissues, immersed the trunk in a 10 per cent. formalin bath. After a sufficient number of days, transverse sections were made which illustrated with great clearness the extent to which the pleural accumulation itself extends about and over the bodies of the vertebræ, pushing before it the contents of the mediastinum. The accompanying Figs. 1, 2, and 3 illustrate clearly the changes in relations following intrapleural injections of gelatin. Fig. 1 is taken from Braune's *Atlas*, while Figs. 2 and 3 are from the article of Baduel and Siciliano. All sections were made at the level of the nipple.

Comparing the clinical data with the conditions as illustrated by these experiments Baduel and Siciliano come to the following conclu-

sions as to the cause of the sign: Percussion of the vertebral column normally gives a clear note because of the contiguity of the pulmonary parenchyma. This note becomes flat at the lower limit of the lungs. In pleural effusion, however, the fluid not only takes

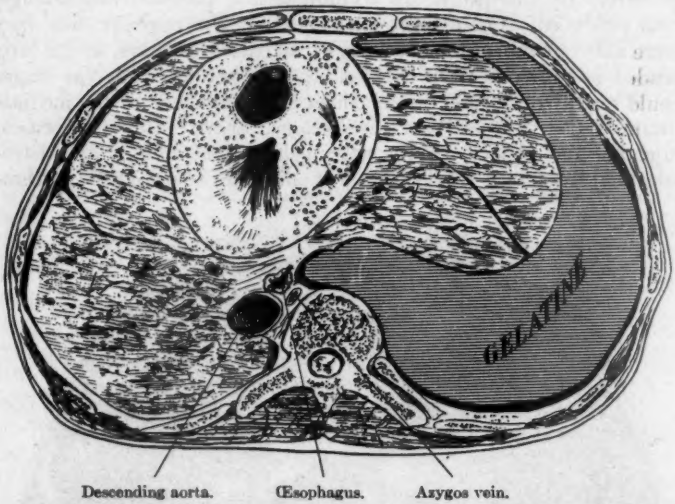

FIG. 2.—Transverse section at the same level as in Fig. 1 in a case of artificially produced right pleural effusion, showing the displacement of the mediastinum and the extension of the pleural contents over the spine. (From Baduel and Siciliano.)

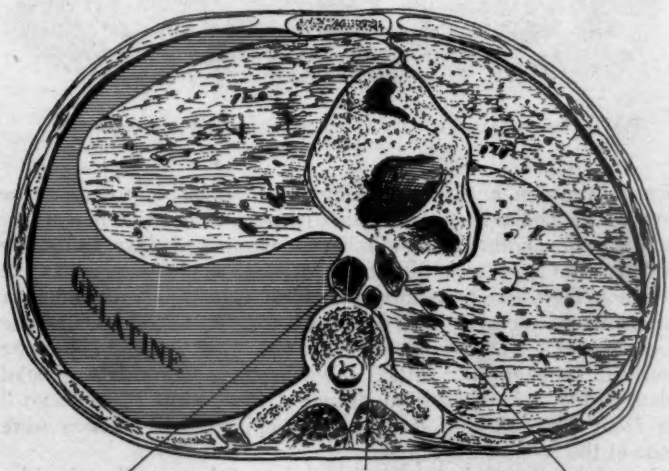

FIG. 3.—Section at the same level as in Figs. 1 and 2 in a case of artificially produced left-sided effusion. (From Baduel and Siciliano.)

the place of one lung, but it extends also anteriorly over the body of the vertebræ, thus inhibiting its capacity for sonorous vibration—that is, it acts as a mute. This dulness extends naturally to a certain extent to the paravertebral region (transverse processes, ribs), especially in the lower part of the chest, where the fluid collects in greater quantity and exercises its action more markedly. In addition to this, Baduel and Siciliano believe that, especially on the left, that is the right-sided effusions, the displacement of the contents of the mediastinum—aorta, œsophagus, azygos vein, and heart—plays a certain part, especially in bringing about a compression of the lung.

Ewart has recently added his testimony to that of the other clinicians already mentioned, as to the importance of this sign. He lays especial stress on the diagnostic value of the variability in the size of the paravertebral triangle with change of position, that is, its diminution or disappearance when the patient lies on the affected side.

Since his first acquaintance with the descriptions of this sign—some two or three years ago—one of us (Thayer) has determined its presence in most cases of pleural effusion which have come to his notice. As time has gone by he has been more and more impressed with the constancy of the sign, the ease with which it may be demonstrated, and its real diagnostic importance. Accordingly, last winter, it occurred to us that it might be of interest to gather together a series of cases of pleural effusion which we had examined with regard to the presence or absence of the paravertebral area of dulness. We fancied, at the outset, that on looking over the histories of the last two years we should find four or five cases in which there were satisfactory records of this phenomenon. Only one such case, however, was found. This instance and thirty-one others which we have observed during the past year, form the basis of the present communication.

Method of Procedure. Although percussion of the paravertebral triangle is a simple matter, it requires care and deliberation, as do all methods of precision. After percussing out the limits of the supposed effusion one should mark out the lower limit of pulmonary resonance on the opposite side and then percuss downward directly over the spine, marking the point at which dulness (relative) begins. It will be found usually that this point corresponds fairly closely with the beginning of relative dulness on the side of the effusion; that at all events it is a little higher than the beginning of flatness. One should then percuss downward along lines parallel to the spine and inward toward the spine along lines parallel to the lower limit of pulmonary resonance. In this manner it is usually easy to mark out, at the inferior and mesial angle of the healthy side of the back, a triangle of dulness. The vertical side of this right-angled triangle, represented by the line of the spinous processes,

reaches to a point somewhat higher than the upper limit of flatness on the affected side. The base, represented by the mesial part of the line marking the lower limit of the lung on the unaffected side, varies, according to the size of the effusion, from 2 cm. to as much as 7 cm. in extent. The third side of this dull area is represented by a line joining the extremities of these two lines. It has sometimes seemed to us, as has been noted by Rauchfuss, that this line showed a slight outward convexity.

Summary of Observations. Of the thirty-two cases with which this report is concerned, twenty-four were instances of pleurisy with effusion. One of these was carcinomatous, and one was associated

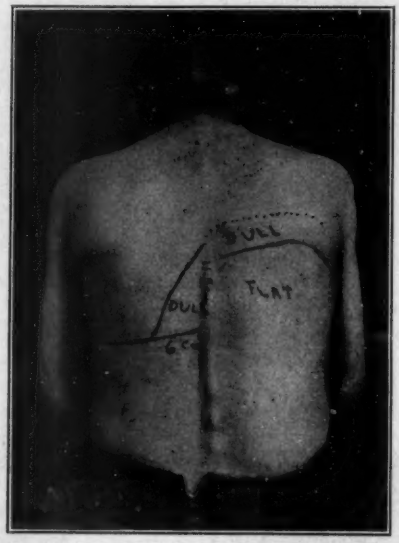

Fig. 4.—Aortic insufficiency; hydrothorax on the right side; paravertebral triangle of dulness on the left.

with a post-pneumonic infarction of the lung. Five were instances of hydrothorax in association with cardiac disease. Three were empyemas; one, post-pneumonic; one, typhoid; one, an interlobular, encapsulated empyema following puerperal infection. In all but one of these instances fluid was demonstrated by puncture or operation. In this case, an instance of infarction following pneumonia, there were signs suggestive of pleural effusion with a well-marked paravertebral triangle of dulness which disappeared later with improvement in the signs. No exploratory puncture was made. In the remaining thirty-one cases a distinct paravertebral triangle of dulness was demonstrated in twenty-nine.

Sex. Of these 29 cases, 19 were men; 10 were women.

The *age* varied from ten to sixty-seven years.

Side Affected. The effusion was on the right side in fifteen cases; on the left in thirteen, and on both sides, alternately, in one.

The *size* of the triangle varied with the extent of the fluid, the apex, when percussion was carefully carried out, reaching a point a little above the limit of flatness on the other side. The base line of the triangle ranged all the way from 3 to 7 cm. in length. The average size was slightly larger in right-sided than in left-sided effusions. In one case (No. 49553) a small, though distinct, triangle was made out in connection with a left-sided effusion, which on aspiration yielded only 250 c.c. of sero-fibrinous fluid. The upper limits of flatness of the effusion reached, in the back, to a point one finger's breadth below the angle of the scapula.

Variation in the Size of the Triangle with Change of Position. This important test was made in but four recent cases (Nos. 55951, 56297, 56479, a case in private practice). In each instance it was found that when the patient lay on the affected side the triangle nearly or entirely disappeared. In view of the fact that in the one case in which a suggestive paravertebral triangle of dulness was demonstrated in a pneumonia, change of position had little or no effect on the limits of the area of dulness, we are inclined to agree with Ewart in regarding this as one of the most important features of the sign.

No definite observations were made with regard to variations in the *vocal fremitus* over the paravertebral triangle. The area is, indeed, so small and the subjacent muscle so thick that it is questionable whether variations in the fremitus could be easily brought out.

The character, however, of the *voice sounds* and *respiration* in Grocco's triangle are interesting. In 8 cases (Nos. 53903, 54097, 55278, 55218, 54731, 56297, 56762, a case in private practice) it was noted that the respiration and voice sounds were diminished in intensity over the area of dulness as compared with the adjacent parts. In five of these cases the respiration was of the same distant, tubular quality as that noted over the effusion, and in several instances the characteristic nasal character of the voice sounds was transmitted across into the area of triangular dulness. In the three cases in which it was tried, the coin sound heard over the triangle had the same clear, metallic ring as over the effusion. This metallic tinkling quality disappeared instantly when one passed out of the triangular area of dulness. In two instances in which a note was made as to the character of the respiration in the triangle, no change could be made out. In the remaining cases, no satisfactory note was made upon the auscultatory signs.

Cases of Pleural Effusion without the Paravertebral Triangle. In two instances of pleural effusion, the paraver-

tebral triangle was not observed. In the first one of these cases an instance of interlobar empyema, its absence, which was easily explainable, was of a certain diagnostic help. This case (53985–19392) was that of a woman, aged thirty-six years, who was admitted on March 3, 1906, complaining of pain in the left back which had come on during the puerperium, three weeks before. There was irregular fever and a marked leukocytosis. Everything pointed to some local suppuration. The local physical signs, dulness and suppressed respiration in the left back, were rather indefinite. On March 9 it was noted (Thayer) that flatness began in the left front at the seventh interspace in the anterior axillary line. There was deficient movement of the left chest; dulness throughout the back, amounting almost to flatness below the level of the angle of the scapula. In the dull area the vocal fremitus was almost, if not entirely, absent. On forced breathing there was a distant tubular quality. The voice sounds were distant and not nasal, except in a small area near the spine, where they sounded as if coming through an effusion. The cardiac apex impulse was not felt, but the heart sounds were heard best at a point 6.5 cm. to the left of the median line in the fifth space. Cardiac dulness (relative) extended 4 cm. to the right of the median line. Irregular fever and sweating continued. On March 26 a needle was introduced in several places in the back without result. On the same day it was noted that there was dull tympany at the left apex—a distinct Skodaic note; flatness at the eighth rib in the midaxillary line; deficient movement of the left back; percussion note, dull and high pitched, a little tympanitic as one passed down; not perfectly flat until one passed below the angle of the scapula. Vocal fremitus was felt through the back. *No paravertebral triangle of dulness at the right base.* The respiration in the upper part of the left chest in front was feeble but clear; a few fine rales on cough, increasing in number as one passed downward. Posteriorly, the respiration was enfeebled, of a somewhat tubular modification. Medium and fine moist rales below the spine of the scapular. Below the line of flatness respiration was much enfeebled, as were also the voice sounds; the same medium moist rales were heard following cough.

On April 9 it was noted that the left back was nearly flat; the dullest area lay between the posterior axillary line and a line between the scapular line and the spine. While vocal fremitus was felt along the spine and just inside of it, it was not so well felt a little farther out. The respiration was much enfeebled, distant, and tubular. The voice sounds were feeble over the duller area. *There was no paravertebral triangle of dulness on the right.* The history and physical signs, in connection with the absence of a paravertebral triangle of dulness, and the failure to find fluid on puncture, led to the diagnosis of either pulmonary abscess or interlobular empyema. On April 16 a needle introduced to a

depth of 6 cm., just above the level of the angle of the scapula, revealed purulent fluid. Operation showed an interlobular empyema. The absence of a paravertebral triangle in this case is therefore easily explained; the fluid did not reach the spine.

The second case (No. 53475–19241) was that of a colored woman, aged thirty-one years, admitted to the hospital on January 16, 1906, complaining of abdominal pain and swelling, chills, fever, and sweating. The case was one of tuberculous polyorrhomenitis.

On January 18, 150 c.c. of hemorrhagic, somewhat cloudy fluid was removed from the right pleural cavity. On the following day flatness began at the fourth interspace in the right front, shifting with change of position, over two fingers' breadth. The limits of the dulness in the back were not noted. *No paravertebral triangle of dulness was demonstrable* although it was noted that there might "be a slight dulness in an area scarcely larger than 3 cm. square." Evidence of fluid gradually disappeared, although dulness with rather enfeebled respiration persisted at the right base, probably dependent upon pleural thickening. Examination in this case was made hastily and without great care. Percussion was carried out only to the left of the spine—*not over the spine.* It is probable that a more careful note would have revealed a more definite paravertebral triangle in the area referred to. The amount of fluid, moreover, was evidently small. No aspiration was, indeed, made after this second note, to prove positively the presence of fluid, although the movable dulness would appear to settle the question.

In a third instance the paravertebral triangle, which was demonstrated later, was not found before the first tapping. A. T. G. (No. 54210-19472), a colored waiter, aged twenty-six years, was admitted to the hospital March 21, 1906. There was a well-marked tuberculous pneumonia of the left chest, which, on percussion, was dull above and flat below. The respiration was tubular throughout, but feebler over the lower part of the chest. The vocal fremitus was not wholly absent at the base. *No paravertebral triangle was to be made out.* The heart was distinctly drawn toward the right, relative dulness extending 5.7 cm. to the right of the median line. On the following day, 800 c.c. of clear, straw-colored fluid was removed from the left chest by aspiration.

On April 12 it was noted that there was marked dulness throughout the left back, which was almost flat below the angle of the scapula; in this area the vocal fremitus was suppressed, the respiratory sounds distant, and the voice sounds nasal. *There was a well-marked paravertebral triangle* on the right, the base measuring 4 cm.

This is the only instance among our cases examined in which the paravertebral triangle of dulness was not demonstrated in the presence of a well-marked effusion. Its absence in connection with its subsequent appearance, we are unable to explain. Kernig,

who found the sign constantly in a considerable number of cases, had one experience exactly similar to this.

Two Cases in Which a Paravertebral Triangle of Dulness was Detected in the Absence of a Demonstrable Effusion. In a number of cases of pneumonia and thickened pleura we have failed to detect a paravertebral triangle. Twice, however, the sign was observed in cases in which puncture of the chest failed to reveal fluid.

In the first instance (No. 54731–19642), in which, on entrance, there was a well-marked left-sided effusion with an associated paravertebral triangle of dulness on the opposite side, the base measuring 6 cm., aspiration of 1600 c.c. was followed on the succeeding day by an apparent reaccumulation. Two days later there was flatness to the angle of the scapula of the left side with a distinct paravertebral triangle measuring 9 x 6½ cm. Flatness in front began at the fifth rib in the recumbent posture, rising one interspace in the erect position. The breath sounds were clear in the upper front, feeble below; slight pleural rub in the third and fourth interspaces; voice sounds distant in the dull area. The left back was tympanitic above, flat at the angle of the scapula. The voice sounds were distant in the dull area, and the breathing feeble as one passed from above downward. There were a few crackles at the line of flatness. There was no egophony. Slight vocal fremitus was felt to the left base. The needle was introduced in two places, in the eighth interspace below the angle of the scapula, and in the ninth space. What was believed to be the lung was clearly felt, but no fluid was obtained. Two days later the signs were the same. Three days after this the patient insisted upon leaving the hospital. In view of the absence of fluid on puncture it is difficult to explain the persistence of the paravertebral triangle, unless one assumes that an existing accumulation was missed in the attempts at puncture—that which the sum total of the physical signs, especially the movable dulness in front, would seem to indicate. It may be that the needle was clogged each time with fibrin.

The second case was one in which the history and physical signs suggested pneumonia. The voice sounds in the affected area in the left back were, however, somewhat nasal and the respiration rather feeble. Percussion of the opposite side revealed a long but not very wide paravertebral triangle. The dulness was hardly as definite and marked as in our other cases. The apex, moreover, did not reach to the upper limit of the physical signs. *On change of position there was little or no change in the paravertebral area of dulness.* Exploratory puncture at two different points in the dull area in the left back was without result.

A small strip of dulness on the side opposite a massive pneumonia has been described by several observers. It is possible that the triangular shape may, in this instance, have been due to an accumulation of fibrin in the pleural sinus. The fact that there was no

change in the limits of the dulness on change of position is worthy of note.

Notable Cases. Several cases seem to us to be deserving of special mention. There were three instances of encapsulated pleurisy, in two of which the paravertebral triangle was of real importance from a diagnostic standpoint.

The first one of these cases (No. 54097–19429) was that of a man, aged twenty-six years, who was admitted with pericarditis, with effusion following acute rheumatism. This was followed by pleuritic exudates, first on one side and then on the other. On February 21 it was noted that there was a well-marked area of flatness at the left base, especially in the lower interscapular

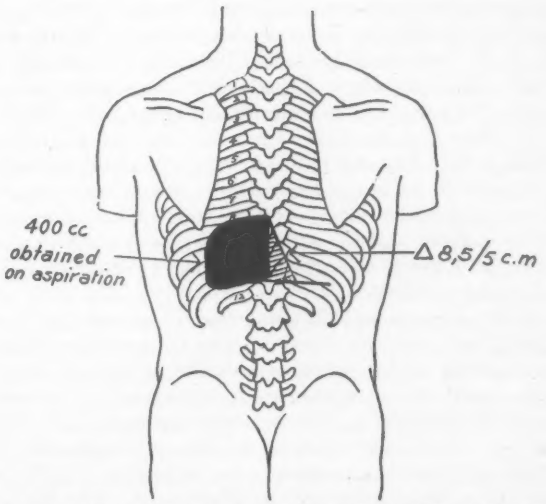

FIG. 5.—Paravertebral triangle in a case of encapsulated effusion. (Case 54097.)

region. Anteriorly to the scapular line, dulness was not marked. Over this area the vocal fremitus was diminished, almost absent; breath sounds distant, slightly metallic, and tubular; voice sounds nasal. The area of flatness as marked out during the visit may be seen upon the accompanying chart (Fig. 5). *On the opposite side there was a well-marked paravertebral triangle of dulness, the upper limit,* 8.5 *cm. from the base of the right lung, corresponding exactly to the area of flatness on the right; the base,* 5 *cm. in extent.* In the triangular area at the base of the right lung the voice sounds were nasal and the breathing tubular and feeble, of the same character as the sounds over the flat area in the left back. By aspiration, 400 c.c. of yellow fluid, with numerous leukocytes, was

obtained from the flat area on the left. Eleven days later, the resonance had cleared up on the left side, the flatness on the right side reached the tenth rib, while on the left a triangular area of dulness, 6 x 4½ cm., was to be made out. In a word, following the disappearance of the accumulation on the left side, there appeared a right-sided effusion with the development of a paravertebral triangle on the opposite side. Thus, in a single case, *the paravertebral triangle of dulness appeared successively on opposite sides of the chest.*

The second case (No. 54292) was that of a woman, aged forty-three years, admitted with acute lobar pneumonia. Before the resolution of the pneumonia, the temperature rose again, and on April 9 it was noted that there was dulness throughout the left back; the breath sounds were distant and feeble, tubular in the region of the left upper lobe and in the interscapular region. The voice sounds over the back were distinctly nasal. There was no absolute flatness in the left side of the chest. Just below and outside the angle of the scapula the voice sounds were almost egophonic. *On the right side of the chest a paravertebral triangle of dulness, measuring at its base about 3 cm., was clearly made out.* A needle, introduced in the lower part of the back, revealed pus, which was evacuated by the surgeon on the same day. Here an unresolved pneumonia complicated the picture and the presence of a paravertebral triangle of dulness of the opposite side was an important element in leading us to the diagnosis of effusion.

The third case (No. 54593) was that of a man, aged twenty-three years, admitted on April 22 with a severe typhoid fever. On May 10, with the patient lying on his left side, there was flatness below the angle of the right scapula with tympany above. The flatness ended sharply at the posterior axillary line. Over the flat area the vocal fremitus was diminished; respiration distant and tubular. There was a somewhat metallic quality to the respiratory murmur and the voice sounds were nasal. On the left *there was a paravertebral triangle of dulness measuring* 8 x 5½ *cm.* A needle introduced into the dull area on the right brought cloudy, purulent fluid. Operation revealed an encapsulated empyema.

In this case the demonstration of the paravertebral triangle was of material assistance in the diagnosis of an encapsulated empyema.

Conclusions. 1. In thirty-two cases of pleural effusion a paravertebral triangle of dulness at the base of the opposite chest (Grocco's sign) was clearly demonstrated in thirty. In one of the remaining cases, an instance with a small effusion in which the examination was rather hastily and imperfectly made, but a small, indefinite area of dulness was noted. In the other case the absence of the paravertebral triangle was easily explained by the position of the exudate—an interlobar empyema. In a third instance, in which a triangle was demonstrated later, it was missed

on the first examination. The sign, therefore, may be regarded as practically constant in cases in which there is free fluid in the pleural cavity, or in which an encapsulated effusion impinges on the spine.

2. This triangle is an area of relative dulness, the vertical side of which is represented by the line of the apophyses of the vertebræ, the apex reaching a point somewhat above the level of flatness of the effusion; the base is formed by the lower limit of pulmonary resonance on the healthy side for a distance of from 2 to 7 cm. from the spine; the hypothenuse, by a line connecting these points. This last line shows, sometimes, a slight outward convexity. The dulness is more marked as one approaches the spine.

3. In the triangular area of dulness the respiratory murmur is often suppressed and of a quality similar to that heard over the effusion. Egophany or a nasal quality of the voice sounds may also be present. The coin sound, when the manœuvre is carried out by placing the coin on the front of the chest below the level of the effusion, shows the same metallic ring as that which is observed over the affected side. These signs may be so marked as to make it possible to outline the area of the triangle by auscultation.

4. When the patient lies on the affected side the triangle of dulness diminishes or disappears, and returns again when the erect posture is assumed, or when the patient lies on the other side.

5. The triangle is usually larger on the left side—that is, in the case of right-sided effusions—than on the right.

6. In three cases of encapsulated effusion the presence of a paravertebral triangle of dulness on the opposite side proved of real diagnostic assistance.

7. Our experience justifies the conclusion that the paravertebral triangle of dulness is a remarkably constant and characteristic sign of fluid in the pleural cavity. It further supports the assertion of the discoverer that it may be of particular value in the case of encapsulated effusions. We regard the sign as an important addition to our means of diagnosis of effusions in the pleural cavity.

8. As to its cause, we are inclined to accept the explanation offered by Baduel and Siciliano, namely, that the fluid, lying against and passing anteriorly over the bodies of the vertebræ, acts as a mute in suppressing the sonorous vibrations of the spine. This deadening of the resonance is naturally appreciable for a certain distance beyond the median line over the area occupied by the transverse processes and the first part of the ribs. It is more marked and extends over a wider area at the base, where the fluid, collecting in the sinus of the pleura, comes into wider contact with the vertebræ and pushes farther around toward the opposite side. The displacement of the contents of the mediastinum—aorta, œsophagus, azygos vein, heart—may play a part, especially in effusion on the right side of the chest, in producing this dulness as well as in bringing about a certain degree of compression of the lung on the opposite side.

9. Although there may be a small strip of dulness along the spine on the side opposite a pneumonia, we have but once detected anything approaching a paravertebral triangle. In this instance the dulness was not very definite and showed little or no change on change of position.

ADAMS-STOKES DISEASE (HEART-BLOCK) DUE TO A GUMMA IN THE INTERVENTRICULAR SEPTUM.

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The condition at present recognized as the Adams-Stokes syndrome was first described by Adams[1] in 1827, and more fully studied by Stokes[2] in 1846. Since that time many cases have been reported and studied, but until very recently no really convincing demonstration of the etiology and pathological basis of the condition had appeared. Thus, Charcot held that the lesion was to be found in the medulla; Stokes himself suggested the heart muscle; Huchard[3] held that the circulatory mechanism of the heart, together with disease of the cerebral vessels, should be held accountable; Gibson[4] and Jacquet[5] called attention to a certain similarity with intermittent claudication; and others have ascribed the condition to fatty degeneration of the heart, to tumors of the vagus, or to pressure upon the pneumogastric nerve. Gaskell[6] was the first to demonstrate the fact that, in tortoises, constriction of the circular layer of muscle at the auriculoventricular junction inhibits the normal rhythm of the heart, so that the auricles and ventricles beat independently

[1] Dublin Hosp. Reports, 1827, vol. iv, 396.
[2] Dublin Quart. Jour. Med. Sci., 1846, ii, 73.
[3] Traité du Maladie du Coeur.
[4] The Nervous Affections of the Heart, 1904, p. 65.
[5] Deut. Arch. f. klin. Med., lxxii, No. 2.
[6] Jour. Physiol., 1883, iv, 43.

of each other. Chauveau,[7] Vaquez and Bureau,[8] and Moritz[9] have contributed interesting articles dealing with the dissociation of the auricles and the ventricles.

To Erlanger[10] belongs the credit of first suggesting that the lesion of Adams-Stokes disease lay in the bundle of His, and of offering incontestable experimental evidence supporting his belief. In 1905 Stengel[11] made a preliminary report of a case of Adams-Stokes disease in which the autopsy disclosed macroscopically an atheromatous lesion on "the anterior mitral leaflet toward its base and aortic edge," being, therefore, in the region "exactly over the bundle of His where this band passes from the ventricle to the auricle." Thus far there has been no report of the microscopic findings, so that it is still uncertain whether there was actual involvement of the bundle, although there is strong presumptive evidence that such was the case.

For many years an active discussion has been carried on by physiologists as to the cause of the rhythmic activity of the heart. One school—the followers of the myogenic theory—has held that the heart muscle itself possesses an inherent automaticity, which is influenced by, but not dependent upon, the nervous mechanism. The other school took the opposite view, namely, that the nerves and ganglia are of primary importance. Long ago the fact was pointed out that contractions occur in the fœtal heart before its nervous structures are developed, and this has tended to support the myogenic theory.[12]

It has been demonstrated by the experiments of Gaskell, His, Tigerstedt, and Erlanger that the symptoms of Adams-Stokes disease and those of heart-block, brought about by injury to the bundle of His, are very similar. Erlanger, by an ingenious clamp screw applied to the muscular bundle, was able to bring about a gradual failure of conductivity from auricle to ventricle. When slight pressure was made the ventricle would miss every fourth auricular stmulus; when the pressure was further increased, the ratio would fall from 1 to 3 to 1 to 2, and finally complete dissociation of the rhythm would occur. In other words, a condition of complete heart-block had occurred, and the ventricle setting up a rhythm of its own contracted entirely independently of the auricle. "With each change in rhythm the blood pressure was much affected, falling with the fall of the ventricular rate and rising with its increase. But even in complete block a fair pressure might be maintained. With partial block both auricle and ventricle might be inhibited by

[7] Rev. de Med., 1885, v, p. 161.
[8] Compt. rend. du Soc. Biol., Paris, 1893, p. 170.
[9] St. Petersburg med. Woch., 1897, p. 301.
[10] Jour. Exper. Med., November 25, 1905; Ibid., January 25, 1906, p. 8; Bull. Johns Hopkins Hosp., June, 1905.
[11] Amer. Jour. Med. Sci., 1905, cxxx, 1083.
[12] Erlanger, Jour. Amer. Med. Assoc., 1906, June 2, 1895.

stimulation of the vagus as easily as under normal conditions. But when the block was complete no diminution, or only a slight diminution, of the rate of the ventricle resulted from stimulation of the vagus. The auricles reacted normally to vagus stimulation. Section of both vagi had little or no influence on the rate of the ventricular beat when the block was complete. But stimulation of the accelerator nerve usually increased the rate of the ventricle. The reaction of the auricles to stimulation of the accelerator nerve was not influenced by the block."

In mammalia the muscular structure of the auricle is separated from that of the ventricle by a layer of connective tissue. In order to substantiate the contention of the upholders of the myogenic theory of cardiac rhythmicity it was essential that some bridge of connecting muscular tissue be demonstrated. This was accomplished by Wm. His, Jr.,[13] and by Stanley[14] independently of each other. But His was the first to succeed in sectioning this muscular bundle, and bring about a dissociation of the auricular and ventricular rhythm.

Owing to the meager character of His' preliminary publications which appeared in 1893, the subject attracted little attention until 1904, when the existence of the bundle, its physiological properties, and its exact anatomy were confirmed through the researches of Retzer,[15] Breunig,[13] Humblet,[17] and Hering.[18]

The structure which is now known as the bundle of His consists of a narrow band of fibers 18 mm. in length, 2.5 mm. in width, and 1.5 mm. in thickness, extending from the right auricle and its valves to the interventricular septum.

More recently the structure has been carefully studied by Keith[19] and Tawara.[20] The latter has given a developmental as well as an anatomical description of it. According to him the "bundle of fibers passes forward from the coronary sinus through the interauricular septum to the central fibrous body of the heart, on which it forms a plexus. One of the bundles from this plexus breaks through the fibrous body into the interventricular septum and is distributed subendocardially on the right and the left sides of the latter. The auricular part of the bundle is made up of very fine, richly nucleated fibers, and the fibers of the ventricular part belong to the Purkinje type."[21]

Still further corroboration of the auriculoventricular dissociation

[13] Arbeit. a. d. Klin. zu Leipzig, 1893, p. 23; Zentrbl. f. Phys., 1895, ix, 469; Deut. Arch. f. klin. Med., 1899, lxiv, 316.

[14] Jour. of Physiol., vol. xiv.

[15] Arch. f. Anat., 1904, p. 1.

[16] Arch. f. Physiol., 1904, suppl. 1.

[17] Arch. internat. d. Physiol., 1904, i, p. 278.

[18] Pflüger's Archiv., cviii, p. 267.

[19] Lancet, 1906, i, 623.

[20] Vide Aschoff, Münch. med. Woch., September 26, 1905; Centrbl. f. Physiology, 1905, xix, 70, 298.

[21] Ewart, Progressive Medicine, September, 1906.

which occurs in Adams-Stokes disease has been furnished by Gibson,[22] who has studied the electromotive changes in a case of heart-block by means of Waller's apparatus. By this method the electric variations are indicated by means of a Lippmann capillary electrometer. "Leading off from the basal region of the precordium to the acid, and from the apical region to the mercury, the usual diphasic movements of he capillary column were clearly seen preceding the apex-beat, and evidently resulting from the ventricular systole. But in the interval between these waves other smaller waves were distinctly seen, and can be attributed only to the systole of the auricle."

The electromotive changes have also been most carefully studied by Einthoven,[23] on a still more elaborate scale. Curiously enough the recording instrument was placed in the physiological laboratory while the patient remained in the hospital. The pulsations were transmitted by means of wires. "He employed a specially arranged galvanometer, the movements of which were recorded on a travelling photographic plate, on which two ordinates and abscissæ, representing electric potential and fractions of a second respectively, were simultaneously recorded." In making tracings for a case of heart-block he was able to demonstrate complete dissociation of the auricular and ventricular oscillations. This method, while obviously impractical in a clinical study of cases, owing to the fact that in addition to a complicated apparatus trained observers with a special knowledge of physics, are necessitated, nevertheless presents very accurate and interesting corroboration of other recent investigation.

Symptoms. The cardinal symptoms of Adams-Stokes disease consist of (1) bradycardia, (2) cerebral attacks, and (3) pulsation of the cervical veins, exceeding in rate the arterial pulsation.

The Pulse. In most cases the pulse is habitually slow, sometimes reaching 30 or 20 beats per minute. Often the rate bears a definite relation to that which was normal for the individual in question. Thus, it may be one-half or one-quarter as fast. This is due to the fact that only every other or every second stimulus is able to cross the bundle of His. The arterial pulse is generally regular in rhythm, although arrhythmia is not uncommon. During the acute attacks the ventricular contractions may fall as low as 10, 8, or even 3 beats per minute. Kidd[24] and Laslett[25] found a condition of asystole lasting sixty and ninety seconds respectively. In Stengel's case an interval of two minutes and ten seconds was noted. If the heart is auscultated during these periods one may hear feeble and muffled contractions. These have given rise on

[22] Brit. Med. Jour., 1906, ii, 22.
[23] Arch. neerl. d. sc. exactes, Harlem, 1906, ser. 2, tome xi.
[24] Lancet, February 13, 1904.
[25] Lancet, June 4, 1904.

the part of some authors to the belief that the sounds are due to abortive systoles, too weak to make themselves felt at the wrist. The most generally accepted opinion, however, is that they are due to contraction of the auricles, a condition which, as Gibson and Mallet[26] have long since shown, does produce a definite sound. When simultaneous tracings of the arterial and the venous pulses have been made it has nearly always been possible to prove definitely the etiological agency of the auricle. At times it is also possible to *see* that the jugular pulsation in the neck is synchronous with the doubtful sounds. Maynard's[27] contention, based upon two cases with radial tracings only, that the accessory heart sounds were due to hemisystole, and not to the contraction of the auricles, is not convincing.

The slow pulse in Adams-Stokes disease is due to depression of conductivity in the auriculoventricular bundle. The auricles contract more or less normally, but the ventricle only responds to every other, every second, or every third stimulus. Just upon what the exacerbations of bradycardia depend still is uncertain.

Norfleet[28] has reported a case of Adams-Stokes disease occurring in a man of sixty-nine years, who for over a year had a pulse-rate of 45 or less per minute. With exacerbations of the bradycardia there were convulsive movements. During these attacks the pulse-rate sometimes remained as low as 8 or 9 per minute for periods of twenty-four hours.

The cerebral symptoms consist of attacks of weakness, vertigo, unconsciousness, occasionally convulsive seizures, and at times Cheyne-Stokes respiration. The patient may have an uneasy feeling about the heart, becomes pale and promptly falls unconscious, being practically pulseless at the wrist, and soon breaks out in a clammy sweat, consciousness returning gradually. The attacks may last from a few seconds to several minutes, they may be repeated at varying intervals and anyone of them may end fatally. Upon returning to consciousness the patient often states that he had a nightmare—thought he was dying.

Occasionally attacks like those just described alternate with simple vertigo, but some cases present certain features which closely resemble apoplexy, the patient falling rapidly into a deep coma, with flushed face and stertorous breathing. In one of Osler's[29] cases there was transient motor aphasia. Actual convulsions, as happened in our case, may also occur. When present they are mainly limited to the face and hands, although general epileptiform attacks are not unknown.

In some cases the initial pallor of the face may be replaced by

[26] Jour. Anat. and Physiol., 1879, xiv, 4.
[27] Brit. Med. Jour., 1905, ii, 847.
[28] Medical Record, November 21, 1903.
[29] Lancet, 1903, ii, 516.

congestion. In our case this was a very noticeable feature. A sensation of blood rushing to the head was a marked symptom in Leuchtweis' case. The convulsive attacks occurring in Adams-Stokes disease are probably the result of cerebral anemia. They are apparently similar to those produced experimentally in animals by severe hemorrhage. The apoplectiform symptoms may reasonably be assumed to be due to venous congestion of the brain, a condition which has long been known clinically to be associated with bradypnœa, paresis of the glottis, and spasmodic conditions.

The belief held by Tripier[30] that the convulsive attacks preceded and were the cause of the bradycardia has been definitely disproved by Webster's[31] tracings.

Some cases exhibited features common to other cardiac disorders, such as nocturnal asthma, precordial oppression, pallor, sudation, and dyspnœa.

The case that we report herewith is of very considerable interest: It presented all the cardinal symptoms of Adams-Stokes disease; sphygmographic tracings taken coincidently from the jugular vein, the radial pulse, and the apex beat showed the incoordination of the auricles and ventricles, the former contracting more often than the latter; and at autopsy a growth was found involving the auriculoventricular bundle, which on microscopic examination proved to be a gumma.

According to His, Jr.,[32] dissociation of the auricles and ventricles might be brought about by any one of three conditions: (1) Degeneration of the myocardium of sufficient extent to interfere with conductivity; (2) dromotropic nerve influences—inhibitory impulses—conveyed principally through the agency of the pneumogastric; and (3) localized disease of the auriculoventricular bundle. As the microscopic examination shows, our case belonged to the last named category.

E. B., a white, male, aged thirty years, a native of Ireland, was admitted to the Philadelphia General Hospital May 20, 1906, complaining of vertigo and syncopal attacks.

Family History. Father died from accident; mother from senility, aged ninety years. Mother had seven children; with the exception of one who died of pertussis at four years, all are living and well.

Personal History. Previous illnesses: Pertussis, mumps, scarlatina, and diphtheria in childhood. Typhoid fever in 1895, lasting two months (including a relapse). Ever since then he has had a trifling but persistent cough. The patient was brought up in the country until he was fourteen years of age, at which time he secured employment in a hardware store. At eighteen years he enlisted for three years in the British Army. Afterward he spent eleven years

[30] Rev. d. Med., 1883, p. 1001.
[31] Glasgow Hosp. Reps., 1901, p. 413.
[32] Deut. Arch. f. klin. Med., lxiv, p. 316.

frequently changing his occupation, having for a time been a barkeeper. He then again enlisted, serving in Cairo, India, and seeing actual service in the Boer war. During the last two years he has been a waiter. He has indulged in occasional alcoholic intoxication, but this was exceptional; he has used tobacco to excess. In 1893, he contracted a "chancroid" of the penis, which appeared eight days after intercourse, and lasted eleven days. He received only local treatment. The sores were multiple, he never developed any rash or constitutional symptoms. He has been married two years. His wife has borne two healthy children, and has never had any miscarriages. He has never had any gastrointestinal, or renal symptoms.

Present illness began on May 16, four days before admission, when while riding in an electric car asleep, he had an attack of syncope. He woke to consciousness to find the other passengers looking over him. During the attack he had fallen from his seat. He describes the onset of the attack as beginning with the sensation that blood was rushing to his head, associated with some vertigo which increased. This phase of the attack was very brief, and he was unable to state whether objects seemed to whirl about him, or he about them. He had two similar attacks subsequently on the same day, and on the following day two or three more. He had three attacks on the 18th, and on the 19th had an attack about 1 A.M., while in bed, after a hard day's work. On the day of admission he had attacks every ten or twenty minutes throughout the day.

Physical Examination. The patient is well-developed and nourished. The pupils are equal, and react promptly to light and distance. The ocular movements are normal; the tongue is fairly clean. The chest is well-formed; the expansion equal and of normal extent. The lungs are resonant and clear throughout. The extremities are negative except for decided downward curvation of the finger-nails, and a scar on the right knee, resulting from a former bullet wound.

In the *recumbent posture* the cardiac dulness extends from the right sternal border, and the upper border of the third rib, to the midclavicular line. The apex-beat is fairly diffuse, and is visible and palpable in the fifth interspace. The radial pulses are equal and synchronous. The blood pressure is low—systolic 117 mm. Hg. (Stanton), diastolic 85 mm. There is marked pulsation of the veins of the neck, the rate being about three times as rapid as that of the radial pulse. This pulsation is direct (not transmitted from the carotid) and is slightly arrhythmic. The first sound at the apex is feeble, and it is followed after a fraction of a second by a second sound, apparently muscular in character, which can be clearly differentiated from the normal second sound of the heart, which follows it, and may be heard over the entire precordium. There is a systolic murmur at the apex, which is transmitted toward

the axilla, but not to the angle of the scapula. The ventricular beats are all felt at the wrist. The pulse rate is 48.

In the *sitting posture* the heart sounds become louder, the systolic murmur is more intense, and the irregularity more marked. The radial pulse-rate is unaffected by the change in posture, still remaining 48. The liver can be palpated at the level of the umbilicus.

May 24. The patient has had three attacks since admission, until today, when they have become more frequent, occurring about once every half to three-quarters of an hour. The attacks begin with a sense of fulness of the head, vertigo, and end in syncope; and last altogether about five seconds. In one attack he had twitching of the facial muscles.

May 23. *Ocular examination*, by Dr. Hansell. There is a most unusual condition of the vessels of the right disk. The artery superficial to the vein is distended in an angular shape, and communicates with the large underlying vein by a broad channel—arteriovenous aneurysm. The arteries beyond the disk contain venous blood. The left fundus is healthy, but darker than normal, owing to the number and tortuosity of the veins.

May 28. *Nasal examination* by Dr. Roberts discloses a deviation of the septum toward the left, both bony and cartilaginous. Except for pallor of the mucous membrane there is no other abnormality. The pharyngeal mucous membrane is somewhat glazed and slightly congested.

The larynx and vocal cords are normal.

Urine. 1020, alkaline, no albumin, no glucose; triple phosphates and amorphous urates.

Blood. Hemoglobin, 80 per cent.; erythrocytes, 3,136,000; leukocytes, 7800; polymorphonuclear cells, 77 per cent.; lymphocytes, 23 per cent.

May 25. *Nurse's Report.* During the attacks the patient becomes weak; objects seem to move around; failure of eyesight for two or three minutes; the face becomes red, and the breathing increases in rapidity for a few seconds. He has had two such attacks within an hour. They usually come on after some unusual occurrence in the ward.

3.30 P.M. Another attack; feels flash of heat over body; head is light; eyes heavy; the radial pulse drops several beats. 4.30 P.M. Slight convulsive spell; twitching of hands—head thrown back—duration one minute.

June 3. Patient is out of bed and about the ward. Complains of weakness. No attack for five days.

June 7. Two attacks yesterday. During attacks pulse feeble and irregular. On auscultation heart sounds are fainter. The respiratory sounds increase in depth, rate and intensity. Face flushed—twitching of hands. Some attacks are preceded by rolling of the eyes, which is followed by a tremor of the body and hands,

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the latter quite forcibly at the onset. Attacks sometimes last only from seven to ten seconds.

June 8. Has had a series of attacks. Extremities cold, complains of it; cyanosis; pulse-rate generally about eighteen per minute, increasing at frequent intervals to thirty. After one such acceleration the heart stopped for fifteen seconds. Twitching hands and staring eyes. Patient considered the last a slight attack. Has had frequent attacks during the last twenty-four hours. Vomits a good deal, is very weak.

June 9. Has vomited everything put in his stomach since yesterday. Attacks numerous; asthenia marked. Toward evening he became able to retain peptonized milk, and finally had a restful night without seizures.

June 10. Continued improvement; no more attacks; stomach retentive; appears stronger. At night an attack seemingly like the rest proved fatal. The patient a few minutes before death had been resting quietly.

During his stay in the hospital the patient received in addition to certain drugs administered for their effect upon the gastrointestinal tract, strychnine, nitroglycerin, and sodium iodide. None of these had any effect upon the cardiac condition. The pulse-rate remained unchanged; the attacks were neither retarded nor abated. It is hardly likely that the iodide would have been beneficial even if the patient had lived longer, for as the subsequent microscopic examination of His' bundle showed, there was very great destruction of tissue.

The accompanying tracings (Figs. 1, 2, and 3), taken a few days after the patient's admission, show very distinctly that the bradycardia was due to a disturbance of conductivity. The tracing from the jugular vein proves not only a diminution in the function of conductivity as evidenced by the lengthening of the A–C interval—the length of time required for the stimulus to pass from the right auricle to the left ventricle, but also the fact that many of the auricular contractions evoked no response whatever on the part of the ventricle. In other words, we have to deal with a condition of complete "heart-block," or what is a better term, auriculoventricular dissociation. It is also to be noted that the frequency of the auricular contractions was markedly increased by the forced inspiration which occurred during the later part of the tracing, whereas the ventricular wave underwent no corresponding change. This is, of course, further evidence of disturbed conductivity. In the cases reported by Stengel, Dock,[33] and Finkelburg,[34] the administration of atropine had no effect whatever upon the rate of the ventricular contractions. This is due to the fact that atropine in man, as in animals, exerts its influence upon the heart through depression

[33] Med. News, Aug. 19, 1905.

[34] Deut. Arch. f. klin. Med., April 6, 1905.

of the pneumogastric, which affects the auricles directly, whereas the ventricles, if the contraction stimulus cannot pass through the bundle of His, are uninfluenced by it. In Schmoll's[35] case the administration of atropine reduced the auricular cycle from twelve-tenths to eight and one-half tenths of a second, while the ventricular time underwent no change.

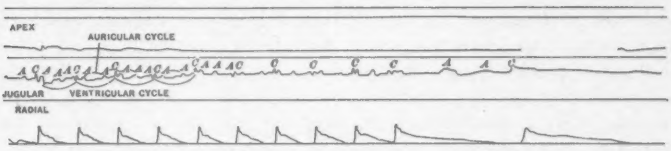


FIG. 1

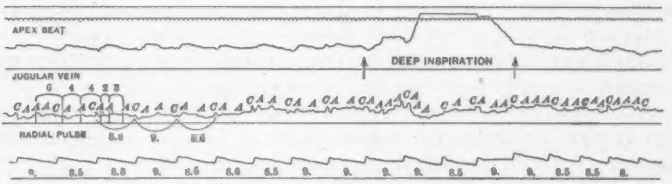


FIG. 2

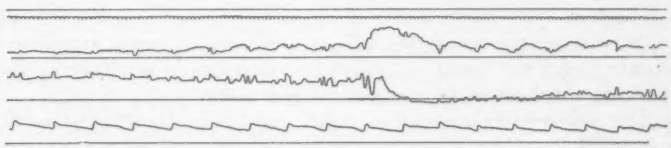


FIG. 3

Cardiosphygmographic tracings. In Fig. 1, during the last two ventricular contractions the speed of the cardiosphygmograph was increased about fourfold. The duration of the auricular cycle varied from four-tenths to twelve-tenths of a second, that of the ventricular cycle from seventeen-tenths to eighteen-tenths of a second. *A*, auricular systole; *C*, ventricular systole. The time marked records one-fifth second.

The fact that the ventricles were not affected by vagus influence was shown by the fact that change of posture on the part of the patient—from the recumbent to the sitting, and from the latter to the standing position—had no influence whatever upon the frequency of the radial pulse. A further study of the tracing shows that the failure of the ventricle to respond to the auricular contraction was not due to any loss of power on the part of the ventricle. The elevations in the systolic phase of the radial tracings are large, powerful, regular in strength, and the blood-pressure is normally

[35] Jour. Amer. Med. Assoc., 1906, xlvi, 361.

sustained. This has also been substantiated by the microscopic examination of the ventricular muscle. The sphygmogram also demonstrates the fact that the accessory heart sounds heard over the precordium between the radial pulses must have been auricular in origin, and were not due to abortive ventricular systoles, since the radial pulse follows regularly each ventricular contraction, as is shown by the apical tracing.

It will be noted that the ventricular cycle required about nine-fifths of a second; the auricular cycle only from three-fifths to six-fifths. The tracing also shows that there is no definite relation between the auricular and the ventricular contractions. If we were simply dealing with a condition of depressed conductivity we should find the A–C interval either constant in time or increasing in length. This is not the case; the A–C interval at the beginning of the tracing steadily decreases in time until the auricle overtakes the ventricle—indicating complete block. In the latter half of the sphygmogram the deep forced inspiration—between the pointers—produced a marked acceleration of the auricular contractions, while the ventricular rate underwent practically no change.

Additional evidence as to the accuracy of the interpretations of the various phases of the jugular pulse in cases of Adams-Stokes disease has been furnished by a number of observers. Ritchie,[36] Gibson, Finny,[37] Villaret, and Brouardel[38] examined their cases by means of the fluoroscope and were able to demonstrate auriculo-ventricular inco-ordination.

Autopsy. The body is that of a moderately well-nourished adult male; weight, approximately 154 pounds. Rigor mortis is marked; cadaveric lividity slight. Panniculus adiposus is moderate. The muscles are of good volume, bright red in color.

The peritoneum contains a small amount of translucent straw-colored fluid. The abdominal organs are normal in position and relations. The spleen weighs 320 grams, and measures 15 x 10 x 6 cm. The consistency is fairly firm; the cut surface dark red in color, and bulges slightly; the follicles are prominent and well-defined; the trabeculæ are moderately prominent. The *liver* weighs 2050 grams; and measures 28 x 23 cm. The surface is smooth, dark reddish-brown in color with lighter mottlings. It cuts with slightly increased resistance; the cut surface shows normal liver markings. In the posterior portion of the right lobe is a spherical nodule 1 cm. in diameter, dark bluish-gray in color, of a spongy consistency. The *pancreas* presents no pathological features. The *stomach and intestines* aside from vascular injection present no unusual features. The *suprarenals* are somewhat smaller than normal; the cortex brownish-yellow. The *left kidney* weighs 190 grams,

[36] Proc. Royal Soc. Edin., 1905, xxv, 1085.
[37] Brit. Med. Jour., 1906, ii, 967.
[38] Arch. d. Méd. Exper., 1906, xviii, 230.

is firmer than normal, cuts with ordinary resistance, its surface does not bulge, and the capsule strips readily. The cortex and medulla preserve their normal relation in width and are well differentiated. Pyramids are dark reddish-purple and streaked, the cortex considerably lighter, showing normal markings. The *right kidney* weighs 250 grams and presents the same characteristics as the left. The *ureters* show no abnormalities. The *bladder* contains a small amount of turbid, yellowish urine. The walls are of normal thickness; mucous membrane deeply injected. The *left pleural cavity* contains 300 c.c. of translucent straw-colored fluid. At the base are a few firm, fibrous adhesions. The *right pleural cavity* contains 100 c.c. of fluid of the same character as the left. The opposed surfaces of both pleural cavities, not involved in adhesions, are smooth and glistening. The *left lung* weighs 690 grams, and crepitates throughout. On section the lung is light pinkish-gray in color. On pressure a considerable amount of slightly blood-tinged, frothy fluid is exuded. The *right lung* weighs 490 grams and presents the same features as the left. The *pericardium* contains about 20 c.c. of translucent straw-colored fluid. The opposed surfaces are smooth and glistening.

The *heart* weighs 510 grams. Both ventricles and the right auricle contain a small amount of cruor and chicken-fat clot lightly adherent to the wall. The wall is somewhat thinner than normal. The right auriculoventricular orifice admits four fingers with ease. The tricuspid leaflets present no pathological features. A small amount of cruor clot is adherent to the wall of the right ventricle. The right ventricular wall measures 4 mm. in thickness. The papillary muscles are of fair size. The cavity of the left auricle is apparently not enlarged. The wall is of normal thickness. The left auriculoventricular orifice admits two fingers with comparative ease. The mitral leaflets show some fibrous nodular thickening along the line of closure. The leaflets are not distorted. The endocardium and myocardium of the left ventricle present, instead of their normal appearance, the following characteristics: excepting in the posterior portion, from the insertion of the mitral leaflets to the apex, there is a mass protruding approximately 4 mm. above the surface of the normal endocardium, considerably firmer in consistency than the cardiac muscle. The involvement of the left ventricle in this mass can be seen in Fig. 4, the area through which the incision (A–B) runs being the portion of the interventricular septum especially affected, and C, D, and E the papillary muscles through which the process has extended. The endocardium in this region is opaque, grayish-yellow, the surface somewhat nodular. As the middle portion (A, Fig. 4) of the interventricular septum is incised, is seen a firm mass, extending from the endocardium 1.5 cm. toward the right ventricle, and containing a number of homogeneous, yellowish, structureless areas, varying in diameter from

0.5 to 2 cm., and surrounding them areas of a grayish translucent appearance. As the upper portion (B, Fig. 4) of the interventricular septum is incised, this mass is seen to involve practically the entire thickness of the septum, presenting on the right ventricular surface of the septum in three nodules, the one (A, Fig. 5) measuring 1.5 cm. by 1 cm., at the base of the papillary muscle of the middle tricuspid leaflet; the second (B, Fig. 5), somewhat larger, a little above this; and the third (C, Fig. 5) at the base of the posterior tricuspid leaflet.

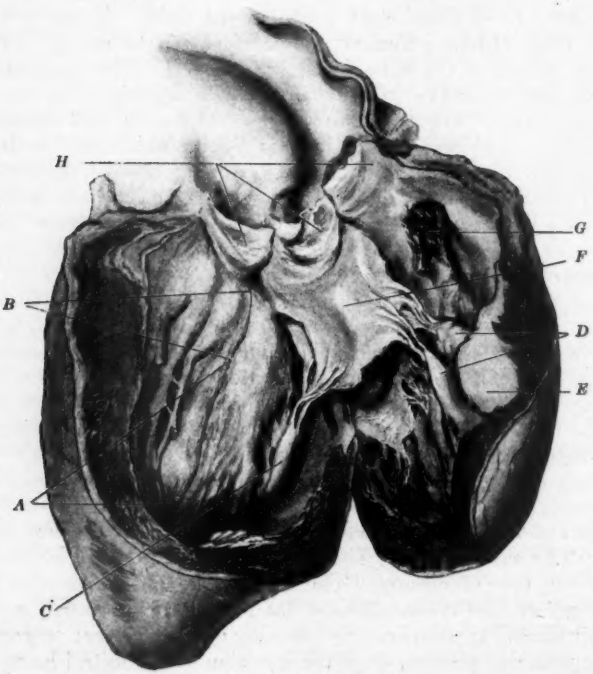


FIG. 4.—The cavity of the left ventricle, showing the gummatous involvement of the wall. *A*, *B*, incision into the gummatous mass, involving the interventricular septum; *C*, *D*, *E*, papillary muscles to which the process has extended; *F*, anterior mitral leaflet; *G*, small clot adherent to the ventricular wall; *H*, aortic leaflets.

All of these nodules consist of a central, firm, homogeneous, yellowish mass, surrounded by dense, grayish, rather translucent tissue. Nowhere within this mass can any tissue be seen of the macroscopic appearance of normal cardiac muscle. At the borders, the demarcation of this mass from the cardiac muscle is comparatively sharp. Upon the posterior superior portion of the endocardium of the left auricle is a thin grayish-red clot, measuring 2 by 1.5 cm., firmly adherent to the endocardium in its central portion. About the

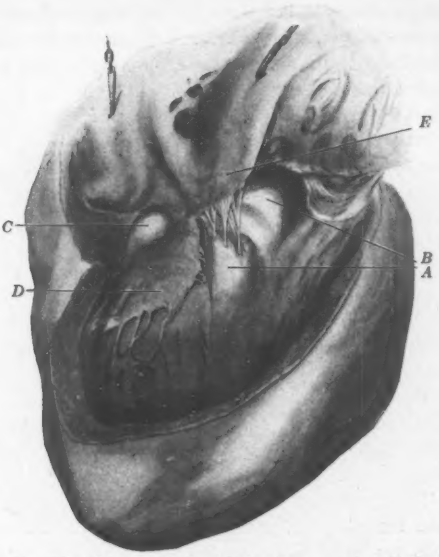


FIG. 5.—The cavity of the right ventricle, showing the extension of the gummatous infiltration from the left ventricle completely through the interventricular septum. *A*, *B*, *C*, gumma presenting on the right ventricular surface of the interventricular septum; *D*, posterior tricuspid leaflet; *E*, middle tricuspid leaflet.

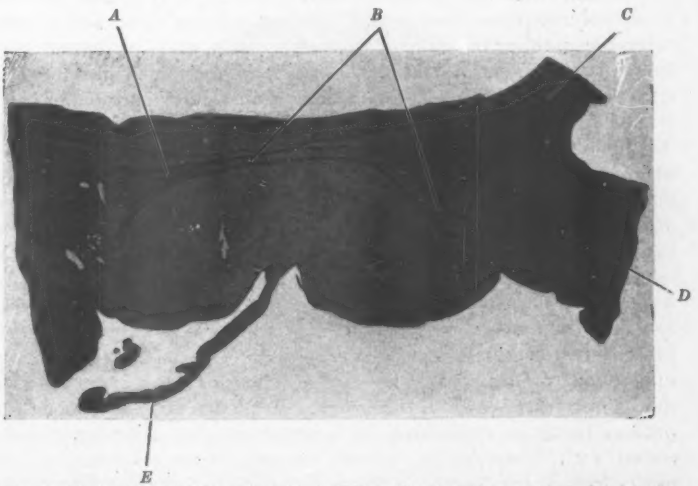


FIG. 6.—Photograph (slightly enlarged) of Section No. 1, with a tracing, showing the course of the bundle of His, from the interauricular septum to its bifurcation. *A*, the bifurcation of the bundle of His; *B*, the course of the bundle; *C*, base of the anterior mitral leaflet; *D*, the interauricular septum; *E*, middle tricuspid leaflet.

middle of the endocardial surface of the left ventricular portion of the interventricular septum is a similar area measuring 0.3 by 0.6 cm. The endocardium under these clots is rough and granular. The left ventricular wall, free from involvement in the mass above described, is 1.2 cm. in thickness. The portions involved in this mass vary from 1.4 cm. to 1.8 cm. in thickness. There are no signs of sclerosis in either coronary arteries or any of their branches as far as they can be followed. Slightly above the aortic leaflets are a few small yellowish areas, pin-head in size. There is no sclerosis and no plaque formation.

The only features of interest in the histological examination of the tissues, excepting those of the heart, are a moderate degree of chronic passive congestion of the spleen, liver, kidneys, pancreas, intestines, stomach, and lung; slight œdema of the lungs; and moderate atrophy of the cortical tissues of the adrenals.

Histological examination of the heart (not including the auriculoventricular bundle of His): The cardiac muscle not involved in the growth above described shows only a moderate amount of fragmentation with slightly decreased prominence of the transverse striations. The portions particularly involved in the pathological process present somewhat varying pictures. In those areas where the process is most advanced there is found centrally a necrotic, homogeneous mass, staining moderately well with eosin, and containing, especially toward the periphery, some nuclear dust. Nowhere within this area is any cell structure preserved. Surrounding this necrotic area is a zone composed primarily of lymphocytes with some polymorphonuclear leukocytes and plasma cells, and a considerable number of young bloodvessels with walls composed of a single layer of endothelium. Toward the periphery numbers of small spindle-shaped cells appear and some larger epithelioid cells, while lymphocytes and plasma cells are still present in small numbers. Young bloodvessels become much more numerous. In a number of areas outside of this zone can be seen one composed of fibrous connective tissue, some of which have undergone hyaline degeneration. In none of these areas are giant cells to be seen. The cardiac muscle immediately surrounding these areas is, in most cases, extensively disintegrated and here and there can be seen a few fibers apparently undergoing hyaline degeneration. The areas in which the process has not proceeded to the stage above described present two pictures. In some of them there is merely a dense infiltration of lymphocytes and polymorphonuclear leukocytes with total disappearance of the normal muscular tissue; in others the normal tissue is moderately well-preserved, but thoroughly infiltrated with lymphocytes, young connective-tissue elements, and newly formed capillaries. The endocardium of the portions of the heart involved in this process is greatly thickened, both the endothelium and the subendothelial layer participating in the thickness,

which is due to a proliferation of endothelial and connective-tissue elements without the signs of an acute inflammatory process. The

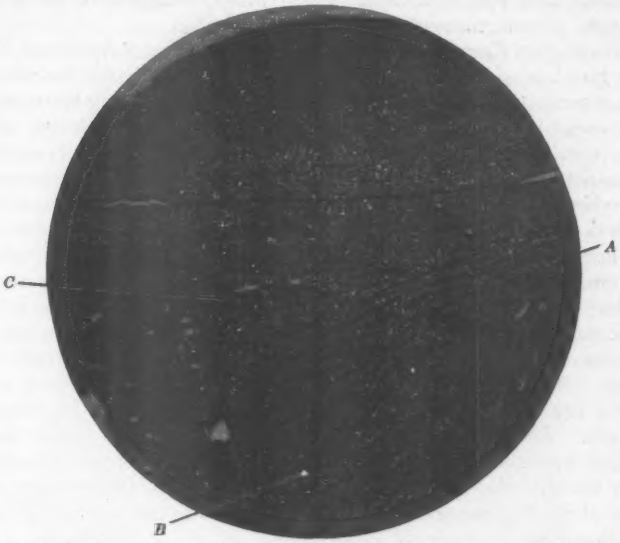


FIG. 7.—Photomicrograph of the bifurcation of the bundle of His. *A*, undivided portion; *B*, the branch to the right ventricle; *C*, the branch to the left ventricle.

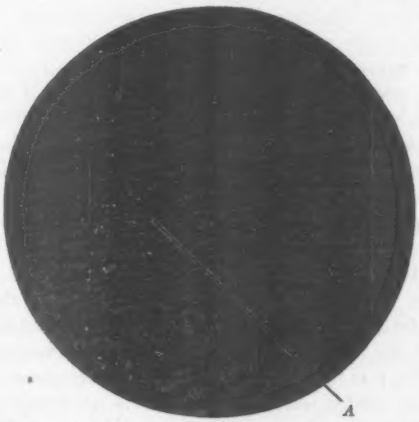


FIG. 8.—Photomicrograph, showing an area of round-cell infiltration in the bundle of His.

pericardium presents no pathological features. A few of the smaller bloodvessels show slight endothelial proliferation. Aside from this, their study reveals no abnormalities.

Diagnosis. Gumma of the heart; acute vegetative endocarditis; chronic passive congestion of the spleen, liver, kidney, intestines, stomach, and lungs; œdema of the lungs; angioma of the liver; bilateral pleural transudate.

Histological Examination of the Auriculoventricular Bundle of His. For histological examination of the auriculoventricular bundle of His, a section of the heart corresponding to the following boundaries was excised: Considering the heart to be placed vertically, with the ventricular septum anteroposteriorly, the anterior boundary corresponded to the middle of the right aortic leaflet; the upper boundary, to a line drawn parallel with the free margin of the aortic leaflets 8 mm. below the uppermost portion of their attachment; the lower boundary, to a line drawn parallel to the upper boundary 1.4 cm. below the lowest point of insertion of the posterior aortic leaflet; the posterior boundary, to the posterior margin of the interauricular septum. The anterior leaflet of the mitral valve and a portion of the median tricuspid leaflet were then cut away from this block. Serial sections in a plane at right angles to the long axis of the heart were cut from this block, commencing at its inferior surface. The sections were 10 microns in thickness. Each sixth section was stained with hematoxylin-eosin; each seventh section with hematoxylin-van Gieson. Subsequently the intervening sections of the first one hundred and fifty were also stained with hematoxylin-eosin.

As the histological findings involving the bundle of His are limited to a series of thirty-nine consecutive sections, we will confine our attention to them. Numbering the uppermost one of these, that is, the one nearest the auricles, 1, the numbers will increase as we approach the apex of the heart. Though in some of the sections above No. 1, portions of the bundle are visible, it is here that it becomes evident throughout its course from the auricular septum to its bifurcation into a right and a left branch. The macroscopic appearance of this section is shown in Fig. 6, in which the course of the bundle, just visible macroscopically in the section, is shown running in a curved direction from slightly above the auriculoventricular septum toward the left ventricular surface of the interventricular septum, then just beneath the endocardium to the point of bifurcation A. Fig. 7 shows the bifurcation into the branch for the right ventricle and the branch for the left ventricle. Though the course of the bundle throughout the first seventeen sections is easily traceable, it is microscopically by no means intact. Especially throughout the undivided portion there is an extensive round-cell and young connective-tissue infiltration. Some of these areas are shown in Figs. 8 and 9. As Section 18 is reached, a much more extensive involvement of the bundle is observed, resulting in a complete solution of its continuity. Here the gumma shown at G in Fig. 10, which is a reproduction of Section 18, has extended

sufficiently to involve the bundle at the point H, Fig. 10, resulting in a complete disappearance of the muscle fibers and their substitution by the infiltrating tissue of the gumma. This interruption in the continuity of the auriculoventricular bundle is shown in Fig. 11. Photomicrographs of the terminations of the two fragments are shown in Figs. 12 and 13. Throughout the remaining sections in which the bundle is visible this interruption persists. Finally, arriving at a level below that of the undivided portion of the bundle, only the right and left branches can be seen, the left lying just beneath and parallel to the endocardium of the left ventricle,

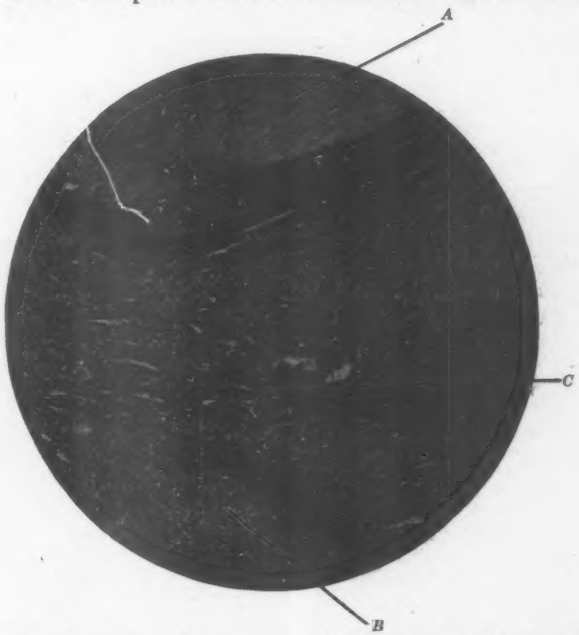


FIG. 9.—Photomicrograph showing an area of round-cell and spindle-cell infiltration in the bundle of His, just as it emerges from the interauricular septum. *A*, auriculoventricular septum; *B*, base of middle tricuspid leaflet; *C*, round-cell and spindle-cell infiltration in bundle of His.

the right showing as a small bundle cut in cross-section lying nearer and nearer to the right ventricular surface of the septum, as we descend toward the apex of the heart.

Though numerous theories have been proposed for the cause of heart-block in the human being, almost all have been without pathological basis. From the recent work in the physiology and anatomy of the heart, we now have every reason to believe that a definite anatomical lesion, involving the bundle of His, is responsible for

this condition in man. On account of the absence of examinations for lesions in the bundle of His in the early pathological reports of cases of Adams-Stokes disease, their consideration in the light of our present knowledge can be practically ignored. The findings looked upon as causal in these cases were probably purely coincidental.

A number of cases have been recently reported with more or less definite pathological lesions involving the auriculoventricular bundle. Stengel has reported a typical case in which there were macroscopically fibrous and calcareous processes at the base of the anterior mitral leaflet involving the area traversed by the bundle of His. Schmoll's[39] case showed scar formation in and around the bundle

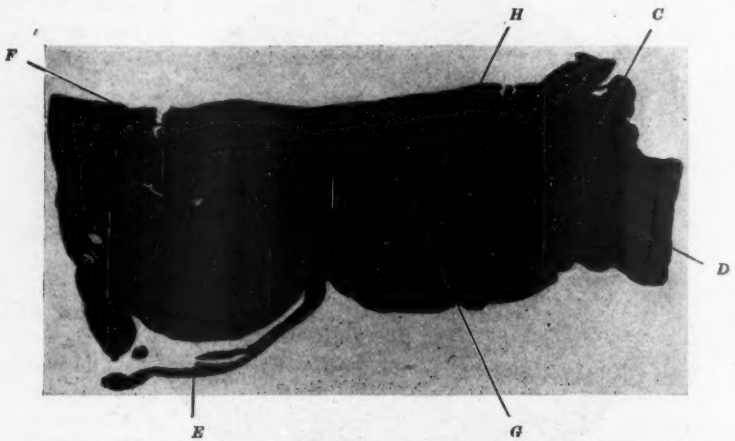


FIG. 10.—Photograph (slightly enlarged) of Section No. 18, with a tracing, showing the location of the interruption in the bundle of His; *H*, location of the interruption in the bundle of His; *G*, the necrotic center of the gumma destroying the bundle at the point *H*; *C*, *D*, *E*, and *F*, as in Fig. 3.

of His leading to atrophy of the muscular elements of the bundle and separation of its fibers from the ventricular muscle. Handford[40] reports a case in which the autopsy revealed gummas, involving the auriculoventricular septum. He does not report the histological examination of the bundle of His itself. The case of Jellick, Cooper, and Ophüls[41] showed anemic necrosis of the muscular septum in the region of the bundle of His consequent upon recent thrombosis of its nutrient arteries. The autopsy of Grünbaum's[42] case dis-

[39] Dent. Arch. f. klin. Med., 1906, lxxxvii, p. 554.
[40] Brit. Med. Jour., December 31, 1904.
[41] Jour. Amer. Med. Assoc., 1906, xlvi, v. 361.
[42] Quoted by Ewart, Progressive Medicine, September, 1906, p. 74.

closed a gumma of the interventricular septum. Keith and Miller[43] report a case which was apparently one of Adams-Stokes disease in which there was found cicatrization of a gummatous mass involving all of the upper portion of the bundle of His and in addition gumma of the coronary sinus, obliteration of the superior vena cava and partial occlusion of the coronary arteries. Sendler[44] saw a case in

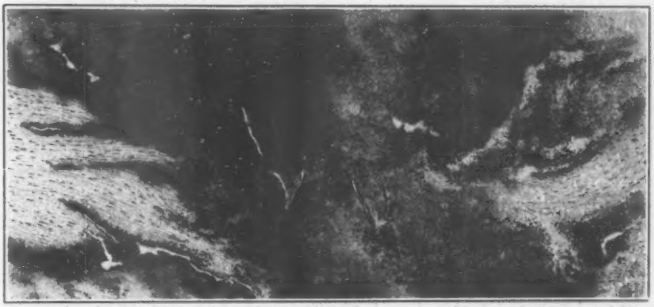
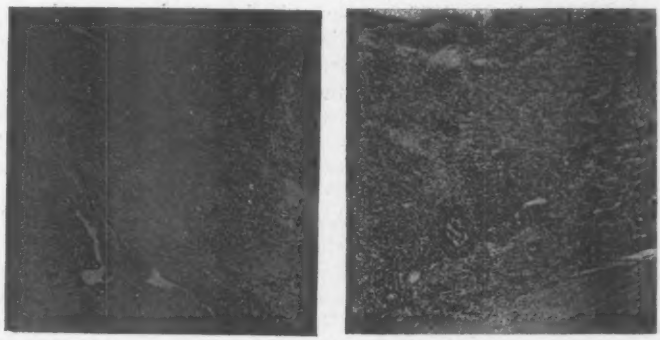


FIG. 11.—The interruption in the continuity of the bundle of His. The two fragments of the bundle are seen entering at the right and left sides of the illustration. Between their two terminations is the infiltrating tissue of the gumma shown at *G*, in Fig. 4. Photomicrographs of the terminations of the two fragments are shown in Figs. 12 and 13.



FIGS. 12 and 13.—Photomicrographs of the terminations of the two fragments of the bundle of His, as shown in Fig. 11.

which a cartilaginous tumor of the interventricular septum was found. The reports of most of these cases have not included the histological examination essential to the determination of the lesion in so delicate a structure as the bundle of His.

[43] Lancet, November 24, 1906.
[44] Cntrbl. f. klin. Med., 1892, p. 642.

The association of syphilis and Adams-Stokes disease appears to have been a peculiarly frequent one. Aside from the cases of Handford, Keith and Miller, and Grünbaum, quoted above, Jacquet, Osler, and Erlanger report cases in which there was clinical evidence in support of the view that syphilis was responsible for the condition. Erlanger and Jacquet mention this frequency of association, but the latter apparently assumes some obscure relationship between the two rather than the actual gummatous involvement of the bundle, as occurred in our case and apparently also in some of the earlier cases reported.

As in all other pathological conditions, the prognosis in Adams-Stokes disease depends upon its cause. First of all, we must clearly bear in mind that all cases of marked bradycardia are not necessarily instances of Adams-Stokes disease. Bradycardia may result from a great number of causes. Thus, it may occur physiologically from hunger, fatigue, pregnancy, and from individual or family idiosyncrasy. Clinically it is met with during the convalescence from infectious diseases, such as pneumonia, typhoid fever, influenza, diphtheria, erysipelas, etc. Riegel has noted the symptom in many cases of gastrointestinal disturbance, gastric ulcer, chronic gastritis, carcinoma, and jaundice. A slow pulse may also be encountered in diseases of the respiratory tract, notably emphysema, and in disease of the heart or bloodvessels—coronary sclerosis, myocarditis, atheroma of the aorta, and embolism of the coronary artery. It occurs also in renal disease—uremia, hematuria. Occasionally it has been noted in diabetes, chlorosis, or other forms of anemia. Bradycardia also occurs in diseases of the nervous system—epilepsy, apoplexy, meningitis, tumors of the brain, diseases of the medulla, and cervical spinal cord, mania, paresis, and melancholia. It has been reported in diseases of the genital system, and of the skin. Finally comes the important toxic group—tobacco, coffee, alcohol, lead poisoning, digitalis, etc.[45] [46]

So much for bradycardia simplex. In order to make a diagnosis of Adams-Stokes disease we must have not only the slow pulse, but also the increased pulsation of the veins, and the nervous symptoms. It seems quite reasonable to suppose from what we now know of the pathology of the bundle of His that minor grades of auriculoventricular dissociation may exist for years without giving rise to marked symptoms. In other words, the degenerative changes in the bundle are so slight in extent, and so slow in progression, that the patient dies from some other cause before the typical symptoms of Adams-Stokes disease develop. Doubtless the combined studies of the arterial and venous pulses which are now being made by different observers with the Jacquet cardiosphygmograph, the

[45] Grob, Deut. Arch. f. klin. Med., xlii.
[46] Babcock, The Heart and the Arterial System, 1903, p. 624.

Mackenzie polygraph, or other instruments, will in the near future throw much light on this and many other hitherto obscure cardiovascular diseases.

Since it has already been shown that several cases of Adams-Stokes disease have been due to gummas involving the bundle of His, heroic doses of the iodides, if resorted to at a sufficiently early stage, may bring about a cure. This has apparently been accomplished in one case reported by Jacquet and Erlanger. In cases in which the lesions are sclerotic or necrotic in character no expectation of recovery can be entertained and they offer practically no hope of other than a fatal issue.

From the accumulated evidence of those cases of Adams-Stokes disease in which satisfactory tracings have been made it seems that the cases were due to heart-block. Now the question arises, May heart-block exist without producing the symptoms of Adams-Stokes disease? Belski and Mackenzie have reported cases of auriculoventricular dissociation without the symptoms of Adams-Stokes disease other than bradycardia. It follows, therefore, that there must be another factor concerned in the production of the symptom-complex. In all probability the ventricular asystole, which is the cause of the syncopal attacks, is brought about by the sudden occurrence of complete heart-block, for as Erlanger has shown, when the bundle of His is suddenly compressed, ventricular activity is in abeyance for a considerable time, that is, for the time required by this structure to inaugurate its own rhythm. This explanation, of course, is applicable only to cases of partial heart-block. Cases such as ours, in which the block is complete, cannot be accounted for in this way. Schmoll has suggested that in the latter event a condition of ventricular depression of conductivity exists, analogous to that which is present in the bundle of His, while the stimulus production goes on normally. If such a state of affairs existed we should expect to find a definite relationship between the rate of the ventricular contractions before and after the block took place. This has actually been noted in a few cases. Thus in His' case the pulse-rate fell from 36 to 18, and later returned to 36. Once more it fell to 12, and subsequently rose to 24, indicating that the original rhythm was undisturbed, but that it required more than the normal number of stimuli to provoke a response. Similar observations have been made by Erlanger, Cornil, and Schmoll, and are, of course, the exact reverse of those noted by Hoffman[47] in cases of paroxysmal tachycardia.

In conclusion, we desire to express our indebtedness to Mr. E. B. Krumbhaar, a student in the University of Pennsylvania, for assistance in the histological examination of the heart.

[47] Ztsch. f. klin. Med., vol. xliii, p. 206.

THE PATHOLOGICAL PHYSIOLOGY OF CHRONIC ARTERIAL HYPERTENSION AND ITS TREATMENT.

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The Pathological Associations of Hypertension. Persistent high blood-pressure is a striking departure from the physiological norm of the circulation, and, though only a symptom, and in nowise a clinical entity, yet is itself a cause of such important secondary lesions in the heart and vessels, that it deserves independent consideration.

It is common in nephritis, especially of the chronic interstitial type. It occurs occasionally in arteriosclerosis. In addition it constitutes the chief feature, during life, of a clinical group of cases, which present the same cardiovascular lesions as chronic Bright's disease, but no evidence of renal involvement. In a recent analysis made by me of one hundred and thirty cases showing a systolic pressure over 200 mm. seen in Dr. E. G. Janeway's office practice, 13 per cent. belonged in this category.[1] Autopsy experience bears this out, both my own and that of observers whose competence is evident.[2]

This group, formerly described by v. Basch as latent angiosclerosis, is now named by the French "hypertension arterielle," to which certain German writers object strenuously. It is perhaps better classed as "hypertension of unknown origin," or "hypertension without nephritis." The idiopathic hypertrophy of the heart of the older pathologists, undoubtedly expressed the same observation, from a standpoint one remove further from the primary lesion.

Its Physiological Mechanism. (*a*) *In Arteriosclerosis.* The hypertension of arteriosclerosis finds the readiest analogy in experiment on the living animal. When the cervical cord has been cut, and reflex vasoconstriction excluded, ligature of the abdominal aorta will raise blood-pressure only when above the origin of the cœliac axis.[3] In accord with this are Hasenfeld's[4] and Hirsch's[5] observations on cardiac hypertrophy. In arteriosclerosis they found this only when there was involvement of the splanchnic vessels, or the thoracic aorta. That the conditions are far from

[1] Amer. Jour. Med. Sci., 1906, cxxxi, 772.
[2] Krehl, L., Deut. med. Woch., 1905, xxxi, p. 1872.
[3] v. Besold, Untersuchungen über die Innervation des Herzens. Leipsig, 1863, pp. 223–229, and Ludwig und Thiry, Sitzungsber. d. Kais. Akad. d. Wiss., math. naturw. Cl., 1864, vol. xlix, 2, p. 442.
[4] Deut. Arch. f. klin. Med., 1897, vol. lix, p. 193.
[5] Ibid., 1900 vol. lxviii, p. 55.

simple is evident, since Marchand[6] has adduced many similar cases in which hypertrophy was lacking. His observations were not by Müller's method, but I think few pathologists will dispute them. My belief is, that the nutritive factor in the production of hypertrophy should receive more consideration. In arteriosclerosis especially, changes in the coronary arteries and the degenerative tendencies of age make a poor basis for the development of new cardiac muscle. One must also bear in mind the demands made on the circulation by the individual, and the possibility of atrophy in a previously hypertrophied heart, after prolonged physical and mental rest in a hospital ward. Autopsies show terminal pictures, which are not a secure basis for too wide inference as to conditions which may have obtained years before.

Certainly in the small number of patients in whom arteriosclerosis leads to persistent high blood-pressure, the latter must be a physiological necessity for the maintenance of an adequate abdominal circulation.

(*b*) *In Nephritis.* The problem of nephritic hypertension is much more complicated. Physiological experiment has sufficed to put out of court the simpler mechanical theories, such as Traube's, since ligation of the abdominal aorta just above the renal arteries does not raise blood-pressure. The simpler chemical theories of stimulation of the heart and vasomotor mechanisms by retained metabolic waste products (Johnson) also must be abandoned, since hypertension is most frequent in that type of nephritis in which the least retention occurs.

The anatomical lesions found in the smaller arteries seem adequate to produce the hypertension in many of the chronic cases which come to autopsy. I believe that thickening of the intima and muscularis, throughout the splanchnic arterioles, plays a large part in the perpetuation of the hypertension, just as cardiac hypertrophy does; but it may be, and probably is, equally its result. Hypertension has been observed within twenty-four hours of the onset of acute scarlatinal nephritis,[7] when anatomical changes in heart and vessels are out of the question.

A purely anatomical increase in peripheral resistance is extremely improbable, in the light of the prompt response to vasodilators in many of these cases. For instance, a woman in my wards at the City Hospital, in whom neither nitroglycerin nor anything else had the slightest effect on the average level of blood-pressure, responded to three doses of nitroglycerin of $\frac{1}{60}$ grain each, five minutes apart, given for the relief of nasal hemorrhages, by a drop from 195 to 95 mm. Any explanation, consonant with such facts, must recognize increased vasomotor tone as a predominating factor.

[6] Verhandl. d. 21ster Kongr. f. in. Med., 1904, pp. 54-58.

[7] Butterman, Deut. Arch. f. klin. Med., 1902, lxxiv, 1.

Increased viscosity of the blood has been suggested as an explanation, but has failed of proof in cases examined.[8] The return to one of Bright's original suggestions, that primary stimulation of the heart may be the cause of its hypertrophy, as Senator[9] advocates, need not detain us in discussing hypertension, for a hypertrophied heart alone cannot produce highblood-pressure, in the presence of a normal splanchnic circulation. This is evident from our knowledge of the regulatory powers of the splanchnic vasomotor system, and comes out clearly in such experiments as Israel's.[10]

Take it all together, a theory recently advanced by Loeb,[11] from Krehl's clinic, seems to accord with more ascertained facts than any other. Observations on the relation of glomerular changes to hypertension, both in acute and in chronic cases, convinced him of the striking parellelism of the two. Most observers would, I think, agree with him, that hypertension, or cardiac hypertrophy, is seen with those types of nephritis in which the glomeruli are extensively diseased (we must except amyloid disease, of course, in which the circulation within the glomeruli may not perhaps be so much interfered with, and in which the nutritive conditions are insufficient for the development of added heart force). The functional activity of the kidney is dependent on the quantity of blood flowing through the glomeruli in a given time. Normally, increase in the rate of flow can be produced by local vasodilatation, as in all glands. With marked increase of capillary resistance within the glomeruli, however, it is unlikely that this should suffice; therefore, Loeb postulates a stronger demand from the glomeruli, which goes beyond the local vasomotor system of the kidney, and, reaching the cerebrospinal centres, calls forth a reflex splanchnic vasoconstriction which increases the general blood-pressure sufficiently to maintain a normal rate of flow through the diseased glomeruli. Such a reflex splanchnic vasoconstriction evoked by the glomeruli, when coupled with a more gradual development of permanently increased peripheral resistance and heart force, through secondary hypertrophy of the arterial wall and the heart muscle, and subject to augmentation, as metabolic end products accumulate in the blood and call for still greater functional activity from the remaining kidney tissues, seems to me very plausible.

Hypertension of Unknown Origin. Clearly little can be said in these cases. Krehl[12] has observed extensive lesions in the brain arteries, and Loeb suggests the possibility of a vasoconstrictor reflex from this and other organs similar to that hypothecated to explain nephritic hypertension. For the brain, our knowledge of

[8] Hirsch u. Beck, Deut. Arch. f. klin. Med., 1902, lxii, p. 560.
[9] Die Erkrankungen der Nieren, Wien, 1902, pp. 110–129.
[10] Virchow's Arch., 1881, lxxxvi, 299.
[11] Deut. Arch. f. klin. Med., 1905, lxxxv, p. 348.
[12] Deut. med. Woch., 1905, xxxi, p. 1872.

the enormous rise in pressure produced by anemia of the medulla (Kocher, Cushing) and of the dependence of the brain circulation upon the general blood-pressure make this far from improbable.

HYPERTENSION A COMPENSATORY MANIFESTATION. Whatever be the exact mechanism of its production, we cannot avoid the conclusion that hypertension expresses an attempt of the organism to maintain an adequate speed of capillary flow through the kidney or other important organ, which would be impossible without it. True, it is a symptom of disease, but still more truly is it a proof of the body's defensive reaction against the disease. This conception is the foundation of any rational treatment.

EFFECTS AND DANGERS OF HYPERTENSION. Nevertheless, there is quite a different aspect to the matter. Persistent high blood-pressure, however necessary, must be followed by important changes, both in structure and function, of the circulatory organs. Hypertrophy of the left ventricle is the most obvious consequence, but many so-called arteriosclerotic changes of Bright's disease are probably equally secondary. Functionally, the circulation at high pressures shows several marked deviations from the normal. The diminishing distensibility of the arteries, as the pressure within them rises, causes an increasing systolic elevation of pressure and suddenness of the pulse wave, which greatly favor arterial rupture at any weakened point. Then, too, the vasomotor regulation is impaired, and ordinary physiological rises in pressure tend to become exaggerated, often bringing attacks of anginal pain in their train. In addition crises of hypertension may appear from causes little understood, as in acute uremic seizures.

The danger most to be anticipated is the gradual development of insufficiency of the left ventricle. Then inadequate capillary circulation, on the one hand, intensifies the primary trouble; and pulmonary venous stasis, on the other, brings dyspnœa on exertion, cardiac asthma, or œdema of the lungs in its train. Later, if the right heart also fail, general venous stasis dominates the picture, and the arterial pressure falls, sometimes to a striking degree.

THE THERAPEUTIC INDICATIONS. From the consideration of these two aspects of hypertension, as a compensatory effort, and at the same time a disturbing factor in the circulation, three lines of treatment suggest themselves: Preventive, adjuvant, and emergent.

(*a*) *Preventive Treatment.* Preventive measures must be directed mainly toward limiting or ameliorating the primary disease, and hence, its effects on the circulation. They are comprised in the general hygienic and dietetic treatment of chronic nephritis. The effect on the blood-pressure is often striking, especially that of rest and a milk diet in the exacerbations of nephritis, so common in our hospitals. Equally good results often follow the more difficult readjustment of diet and mode of life in middle-aged high livers,

who are in the early stage of the disease, a return of the blood-pressure to nearly normal limits being possible. Allbutt has preached this insistently. Massage belongs among the preventive measures and often seems of value. The iodides, I think, must also come in this category. More definite measures, from the standpoint of the blood-pressure, are the avoidance of all markedly hypertensive influences, such as excessive or unusual physical or mental work, straining at stool, and the excessive use of tobacco.

(*b*) *Adjuvant Treatment.* The adjuvant treatment of hypertension is beginning to receive the recognition it deserves. Formerly the discovery of high blood-pressure was too frequently the signal for the attempt to reduce it at any price. Fortunately, as Krehl has lately said, such efforts were usually unavailing. This failure of vasodilators to reduce the general level of pressure in such cases has usually led to loss of faith in the drugs, rather than to an appreciation of the struggle of the organism to maintain its life in spite of the physician. We begin to know the physiological necessity better, and to view with alarm any fall in pressure which is not the result of preventive treatment and the accompaniment of other evidence of improvement. As a rule, such a fall marks the onset of cardiac insufficiency and calls for digitalis, our mainstay in combatting asystole. Not even in mitral insufficiency do more brilliant results follow digitalis therapy than in the failing heart secondary to hypertension; and an increasing blood-pressure, though not invariable, for the conditions are complicated, usually presages a winning fight. The indications for digitalis, and its congeners, are the same with hypertension as without, and no blood-pressure reading should make us hesitate to administer it.

(*c*) *Emergent Treatment.* Emergent treatment includes all the means used to forestall or cut short those dramatic moments which may come without warning to any victim of hypertension when life suddenly hangs in the balance. Here the vasodilators find their proper place and rational use, and are as indispensable as is digitalis, when the indications are for adjuvant treatment. Nitroglycerin and the other nitrites are the most efficient for the relief of the anginal seizures which often follow exertion when the arterial pressure is high, and their action sometimes seems magical. In acute uremia, venesection fulfils the double purpose of relief of hypertension, through reduction of blood-volume, and removal of circulating toxic substances. Light chloroform narcosis, so commonly relied on to stop convulsions, produces a fall in blood-pressure.

Dangerous nasal hemorrhages, an occasional accident, may often be checked by nitroglycerin in full doses. With cerebral hemorrhage the conditions are much more complicated, since the hypertension, when intracranial tension is much increased, may be essential to the preservation of life, while at the same time favoring continuance of the bleeding. In many cases the hypotensive

measures, bleeding and vasodilators, seem to do good. Probably in these the hypertension was pre-existent, and the intracranial pressure not much increased in the posterior fossa. That a differentiation is possible clinically between the hypertension indicating beginning anemia of the medulla oblongata and the hypertension which helped produce the arterial rupture, I do not believe, unless previous records of the case are at hand. The former must, under no circumstances, be interfered with.

Attacks of œdema of the lungs, always of great danger and most agonizing to the patient, do not admit of simple explanation or routine treatment. Unquestionably sudden weakness of the left ventricle[18] is a large factor in their production in the patients we are considering. Such an occurrence calls at least for the simultaneous use of rapid heart-muscle stimulants, and of vasodilators to reduce to a minimum the demands on the left ventricle.

In a certain number of patients in whom severe abdominal pains or intense headache was a prominent symptom, I have been struck by the beneficial effect of morphine, both on the general condition and on the blood-pressure. The removal of the reflex vasoconstriction, which pain produces, may explain it; but this factor alone has not always seemed to me adequate to account for the remarkable and sustained improvement in a few cases of this class.

In closing I would emphasize one point strongly. The height of the blood pressure gives no indications whatever for treatment, except along preventive lines. Hypertension is no more to be attacked therapeutically than is a heart-murmur. Only those symptoms which point unmistakably to inadequate maintenance of the circulation, or to sudden threatening of danger, give us the signal to interfere.

INORGANIC LATE-SYSTOLIC PULMONARY MURMURS IN INFANCY AND CHILDHOOD.[1]

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Two years ago at the meeting of the American Medical Association we presented to the Section on Pediatrics a paper on inorganic late-systolic pulmonary murmurs in children. We were stimulated to do this because our observations were not in accord with the

[18] Cohnheim and Welch, Cohnheim's Gesam. Abhandl., Berlin, 1885, p. 593.

[1] Read at the meeting of the American Pediatric Society, 1906.

generally expressed views in the literature relating to this subject, and especially because of the almost universal statement in the text-books on pediatrics that functional cardiac murmurs are extremely rare in children under four years of age, some authors even denying their existence.

In so far as we have observed, the views expressed in the text-books have not changed, and, therefore, we have decided to offer a paper on the same subject to this Society in order to elicit the views of its members as to the frequency of functional cardiac murmurs, the nature of their origin, and their significance. It seems to us that the question is one of great importance, on account of its relationship to the subject of organic disease of the heart, and one concerning which this Society might do well to express an official opinion.

We do not presume to offer anything new, but wish merely to reiterate our impressions as to the frequency of this murmur and our interpretation of its meaning. We have little doubt that it is commonly recognized by pediatrists, but we feel that the text-books, which serve as a medium for educating the profession at large, should be correct in their statements regarding it. Speaking from experience, we are inclined to believe that the average practitioner not only considers this murmur very infrequent, but constantly mistakes it for an indication of organic disease.

From the descriptions in the literature we feel justified in assuming that all murmurs described as functional, inorganic, or anemic, being systolic in time and having their point of maximum intensity in the pulmonary area, are identical with the murmur which we are discussing. The cardiopulmonary and the diastolic functional murmurs and the functional regurgitations, especially the two former, we have found extremely uncommon in early life, and we do not believe that they should ever be confounded with the murmur to which we refer.

It seems a somewhat curious fact that a number of the French and German writers consider the cardiopulmonary murmurs quite common in infancy and early childhood, and that some of them evidently confound them with the type of murmur under discussion. It is especially interesting to note that Hochsinger, who makes such positive statements regarding the so-called "anemic murmurs," is at the same time of the opinion that the cardiopulmonary murmurs, whilst very frequent after the second year, are nevertheless observed during the first year and that this murmur "is a frequent phenomenon in infancy."

There is evidently a diversity of opinion as to what constitutes a cardiopulmonary murmur. The impression we have gained of this murmur is that it is distinctly systolic in time; that it is heard with maximum intensity at the apex and along the left border of the heart; that it has a tendency to greater transmission to the left;

that it is short and whiff-like in character and lacks the soft, prolonged, blowing sound of the late systolic murmur heard in the pulmonary area. The murmur further differs in that it is heard most distinctly toward the end of inspiration, and in that it often disappears entirely at the end of the forced expiration, especially when the patient is recumbent.

Characteristics of the Late-systolic Pulmonary Murmur. The murmur we wish to describe does not occur with the first sound; the first sound is always distinctly audible and the murmur is superadded, as it were, sometimes with a definite interval of silence, and is not uncommonly, especially when it is not loud, mesosystolic in time. This is one of the principal characteristics of the murmur, and unless one studies the systolic interval carefully the soft indistinct forms will be readily overlooked.

This murmur is ordinarily soft-blowing in character; moderately high-pitched; occasionally almost musical, and more rarely low-pitched and rather rough. It varies in duration, sometimes occupying the greater part of the systolic interval, but more frequently its early portion.

Its point of maximum intensity is most often the second left interspace close to the sternal border. It is sometimes best heard a little more to the left and quite frequently over the third costal cartilage; it sometimes has a second point of increased intensity, especially when the patient is examined in the sitting or standing posture, within and above the apex, about midway between the midclavicular and parasternal lines in the third or fourth spaces, depending upon the position of the apex.

The *position of the patient*, the *respiratory act*, and *exercise* have a striking influence upon this murmur. It is always greatly increased in the recumbent posture and frequently heard only when the patient is recumbent; it should never be considered absent unless the patient has been examined in the recumbent, as well as the upright, position. It is best heard at the end of the expiration and sometimes only heard when the breath is held at the end of a forced expiration. It will often disappear when the lungs are filled with air. *Exercise* exaggerates it. It is not uncommon to have the milder murmurs entirely disappear after the patient has remained recumbent for a time, to return again after the patient engages in some mild exercise.

There is great diversity of opinion as to the character of the second pulmonic sound associated with this murmur. In our experience, it has been invariably accentuated, and we do not, therefore, place any dependence upon the character of the second sound as an aid in the differentiation between this and organic murmurs of the heart.

Ordinarily, the murmur is not transmitted over a very wide area. It is occasionally audible only over the second interspace, but more

commonly also over the third and fourth spaces, in or within the parasternal line, just above and within the apex of the heart, and, when it is very loud, it may be heard over the body of the sternum, at the apex-beat, and occasionally even beyond it. Sometimes a murmur similar in time and quality may be heard in the aortic area, but whether this murmur is the same murmur transmitted, or whether it is a different murmur produced by the existence of similar conditions in the aorta, we have not been able definitely to determine. When the murmur is audible over this wide area, it always continues to have its point of maximum intensity in the second left interspace.

The *position of the apex-beat of the heart* is not altered and the *area of heart dulness* is not increased.

There is almost invariably associated with this murmur a loud venous hum over both sides of the neck, commonly audible also below the sternal ends of the clavicles, sometimes over the manubrium of the sternum, and less frequently in the aortic area. In addition to the venous hum, one can quite frequently hear systolic blowing murmurs over the carotid and subclavian arteries.

The *relationship of anemia to this murmur* has been freely discussed in the literature and there exists a great diversity of opinion regarding it. We do not believe that anemia *per se* is responsible for its production, but, unquestionably, the conditions giving rise to the murmur are frequently associated with anemia.

In the series of eighty cases herein reported, we have determined the hemoglobin content by means of the Dare apparatus in all but eight. In three instances, the hemoglobin content was below 60 per cent. There were twenty-three which showed no functional murmurs. The hemoglobin content in these cases was respectively: 65, 70 twice; 71, 75, 78, 79, 80 five times; 81, 83 twice; 88 three times; 89, 90 twice; 92 and 94; whilst in those showing the murmur, there were found such percentages as 80 twice; 83, 85 five times, 87, 88, 90 twice; 92 and 100. There were, however, among these latter, a number of cases showing lower hemoglobin content, as many as 11 having less than 70 per cent. It will be seen from these figures that in very few instances was there a marked degree of anemia, and in one case the murmur was present when the hemoglobin content was 100. Quite often we have failed to find these murmurs present in infants suffering from severe forms of anemia.

We are unable to offer a new theory for the cause of these murmurs. The number appearing in the literature would seem pretty effectually to cover the possible modes of production. There is practically no abnormal condition concerning which more speculation has been indulged in. We have been impressed by the apt description which Balfour gives of the pulmonary area when he refers to it as the "region of romance." We will not discuss all of the theories which have been advanced, but limit ourselves to the consideration of those which seem more or less plausible.

We wish, first of all, to cite the view expressed by Leube. He believes the point of production of these murmurs to be at the base of the heart, in the beginning of the great vessels, especially the pulmonary artery, the point at which they are most distinctly heard. He says: "The wall of the pulmonary artery, being in an atonic condition, dilates more markedly in the systolic pressing in of the blood than under normal circumstances; by this dilatation of the beginning of the pulmonary artery, isochronous with the systole, there are created all of the conditions necessary for the production of the murmur." According to this conception, the time of the murmur would coincide with the time of expulsion of the systole. This represents the second part of the systole and corresponds to the first part of the descending line of the cardiogram, and, therefore, the slight sound which is formed during the systolic closure may be heard for a brief period besides the murmur; that is, it introduces the latter.

R. Geigel's explanation of this murmur is that it is produced by a relatively high ventricular pressure and an abnormally low pressure in the aortic and pulmonary arteries, which prevents the closure of the semilunar valves during the so-called closure period, giving rise to the production of a murmur at the base of the heart, the area of physiological stenosis. Leube is inclined to believe that murmurs sometimes occur in the aortic and pulmonary areas which occupy the entire period of the systole and which can be explained on the basis of Geigel's theory, but that this is not satisfactory for the explanation of the systolic murmur in which the sound of the systolic closure is audible.

Cabot accepts as the most plausible explanation that, as regards most functional murmurs, they are due to a temporary or permanent dilatation of the conus arteriosus or to pressure or suction exerted upon the overlapping lung margins by the cardiac contractions.

Fagge explains them thus: The basis of the two main arteries are supposed to be unable to retreat in correspondence with the diminished volume of the blood in anemia to the same extent as the orifices through which the blood enters them, in consquence of which vibrations occur in the current.

Drummond believes the murmur to be "the result of vibrations generated in the conus arteriosus of the right ventricle, at least in the cases in which its maximum occupies the second and third interspaces close to the sternum on the left side."

Clifford Allbutt "leans to the belief that the solution of the causation of this murmur will be found in some altered relation between the blood and the walls of the vessels, especially the pulmonary artery and conus arteriosus, so that an excessive vibration of the walls takes place."

Rudolf thinks the murmur is caused by the pulmonary artery becoming dilated whilst the orifice remains normal, the blood then

being split up into fluid veins as it passes from the ventricle into the vessel. He does not believe that the dilated conus arteriosus can of itself produce a murmur, but that the pulmonary artery must be dilated at the same time. Otherwise, one merely has a cavity opening into a cylinder which will not give rise to a murmur.

Nixon explains the mechanism of production of murmurs, only audible when the patient is recumbent in those who are not obviously anemic, as due to a diminution of tension in the artery, which allows a twist or contraction to be formed at its root during the ventricular contraction. In this event, the disappearance of the murmur when the erect position is assumed would be explained by the traction made upon the pulmonary artery by the weight of the heart tending to preserve the natural caliber of the vessel.

La Salle has noted that the administration of trinitrin and other vasodilators tends to augment functional murmurs, which corroborates the view that lowered arterial tension plays a large part in their production.

We quote Foxwell's explanation at some length because it seems to combine the views before mentioned and to interpret them in a very rational manner. He says: "We may consider the whole right ventricle as one-half of a cone, which has been described from apex to base. The stout septum ventriculorum forms the triangular surface of the section, and, as the left ventricle does not fail, no more does this septum; hence, we may look upon the ventricle as a triangular board to which is attached a semicircular convexity of rubber. It is evident that this yielding rubber will stretch most where it is least restrained by the rigid triangle, namely, along the semicircular border of its base. Also, that the portion of this border which will stretch most will be the conus, for the lowest part is held in check by the unyielding rigidly fixed inferior vena cava and the middle portion by the chordæ tendinæ of the tricuspid valve and their stout musculi. Further, the direction of the blood current is from the apex toward the pulmonary valves; the conus will tend to give, therefore, most in the direction where it is longest distended with blood.

"Given this dilatation of the conus, that of the pulmonary artery is easily explained. The dilating conus carries the valves upward and this shortens the length between the two extremities of the artery. The artery becomes lax and when distended with blood enlarges in its transverse diameter, so that its wall may occupy the same superficial area. Finally, we must remember the easy distensibility of the pulmonary artery, which is proportionately, after due allowance is made for the different tensions at which they work, some six times that of the aorta."

This explanation appeals to us as one of the most rational given and in a way accounts for the relatively greater frequency of these murmurs in early life. We know that the arterial tension is lower

in children than in adults, and it seems reasonable to suppose, therefore, that conditions having a tendency to depress the arterial tension would make a more rapid and profound impression upon the circulation in early life and that there would, therefore, result a greater tendency to dilatability of the great vessels. Aside from this, it is not unlikely that the higher position of the diaphragm in early life, dependent upon the relatively large liver, the tendency to distention of the abdominal organs, and the undeveloped condition of the lungs, by maintaining the heart in a high position, relieve the tension on the pulmonary artery, to some extent "shorten the length between the two extremities of the aorta," thus rendering it more dilatable.

That the murmur is produced more frequently in the pulmonary artery than in the aorta is probably explained by the fact that the walls of the pulmonary artery are normally thinner and therefore more dilatable than those of the aorta, and by the fact that the resistance to the flow of the blood expressed from the heart is greater and more proximate in the pulmonary artery than in the aorta.

Frequency of Functional Cardiac Murmurs. Of the American text-books, Holt's is the only one which seems to appreciate the frequency of the existence of these murmurs, and we feel that the statements in his work do not do full justice to this phase of the subject. He says: "Accidental murmurs may be due to anemia and other blood conditions and, although not so common as in older patients, they are by no means rare even in infants." He further states that anemic heart murmurs are frequently heard in marasmus.

Koplik quotes Hochsinger as not having found a single anemic cardiac murmur in an examination of two hundred anemic children under four years of age. He states that he has, under exceptional anemic conditions, found a mild, blowing, basic murmur and that one such murmur occurred in a child under four years. He considers the "hemic murmurs" so common in the febrile conditions of adult life as "rarely heard, even in severe febrile affections with anemia in patients under three years." He has, however, heard them in children under three years of age with severe typhoid fever.

Rotch, in referring to this matter, says: "It is rare to meet functional cardiac disturbances before the middle period of childhood, but they increase in frequency as puberty approaches." He includes the inorganic murmurs in this statement. In the paragraph on the symptomatology of anemia infantum pseudoleukemica of von Jaksch, he says "there are often a venous bruit in the neck and functional cardiac murmurs."

Jacobi, in his text-book, says: "The functional murmurs are not so frequent in the child or adolescent as in the adult." In an article appearing in the *Transactions of the American Climatological Association* for 1900, he refers to a systolic murmur which he noted

in an infant, aged thirteen months, suffering from an attack of pneumonia, which disappeared during convalescence. A fatal suppurative pleurisy following the pneumonia permitted a postmortem study of the heart and absolutely nothing abnormal was found in the organ. This he considered a functional mitral murmur.

Keating refers to functional murmurs in early life as "not uncommon."

Caille, in his text-book on *Differential Diagnosis and Treatment of Disease*, says: In children accidental murmurs are comparatively rare.

Cotton makes no reference to the frequency of inorganic murmurs. He says: "The soft, systolic bruit common to infectious fevers, the cardiorespiratory murmur of vesicular emphysema, and the before-mentioned sounds due to anemia and transient incompetency are all encountered in childhood."

Meigs and Pepper considered a certain percentage of the systolic murmurs heard over the body of the heart in chorea, functional in character and dependent upon the associated anemia.

Ruhräh makes the statement that hemic and functional murmurs are frequently heard in anemia and febrile diseases and are often mistaken for organic heart disease.

Churchill in discussing a paper by Butler read before one of the Chicago Medical Societies made the following statement: "At a recent Congress, Soltmann and Hochsinger said that 'hemic murmurs' in children under four years of age were extremely rare and that they were rare even up to eight years. If this statement be true, then there must be a deplorably large amount of organic heart trouble in children."

Morse in discussing the paper which we read before the American Medical Association made the statement that "functional murmurs are very common in infants."

The foregoing quotations represent the only printed statements made by past or present members of the American Pediatric Society, relative to this subject, which we have been able to find.

A few other American authors refer to the subject thus: Taylor and Wells say that the functional or accidental murmurs in childhood, particularly in older children, are of fairly common occurrence. Oppenheim believes that murmurs in children under two and one-half years of age are almost always congenital in origin, and that hemic murmurs are much more likely to occur in young children than those of organic disease.

The opinions expressed in the foreign text-books are very similar to those above quoted. The writers of German text-books seem to have been influenced by the statements of Hochsinger and Soltmann, both of whom, a few years ago, expressed the opinion that functional murmurs are extremely uncommon during the first three years of life and that they are not observed frequently until after the

seventh or eighth year. Hochsinger even went so far as to state that all systolic murmurs heard over the precordium in children under four years of age should be considered organic murmurs.

Frühwald considers them rare in childhood, particularly during the first four years.

Graetzer considers them rare up to the seventh year of age and of very rare occurrence in children under four years of age, but admits their occasional existence even in nurslings. Baginsky makes no special reference to functional murmurs. In a section on anemia, he says: "Venous murmurs are audible in many cases, especially in later childhood."

Henoch believes the accidental cardiac murmurs very rare under four years of age.

R. Hecker and J. Trumpp embody the views of Hochsinger that "the so-called accidental inorganic heart murmurs in children under four years of age are of the greatest infrequency, and a systolic heart murmur with almost positive certainty proves the existence of an organic heart affection, even if it exists as the only provable heart symptom."

Filatou says that "anemic murmurs, although seldom, occur in children under three years of age."

Audeod, in his article in the *Traité de Maladies des Enfants*, says: "One does not find cardiac murmurs in anemic infants, but in the anemias of the second infancy cardiac bruits are common."

Among the English authors of text-books on Pediatrics, Dawson Williams and Ashby and Wright make no reference to the occurrence of these murmurs.

Goodheart and Still refer to them only as associated with chorea.

Hutchinson says that "a loud murmur heard over the precordium under two years is almost certainly congenital. Hemic murmurs may, however, occur in children under two years of age."

John Thomson says: "The functional murmurs are certainly much less common in children than in adults. They do occur, however, occasionally even in young children."

Donkin considers the occurrence of "anomalous and temporary murmurs over the precordia of healthy infants frequent.

In practically all other text-books on the diseases of children which we have consulted there is either no reference made to these murmurs, or if mentioned, the frequency of their occurrence, or the age at which they are most common, is not stated.

The opinions expressed in the journal articles and theses especially devoted to the discussion of this subject are quite similar to those found in the text-books, save that there are more authors who recognize their occurrence, the frequency of their occurrence, and the fact that they are common even in early infancy.

Garrod, for instance, states that murmurs identical in character with the hemic murmur in adults are met with even in very young

children. He refers to an infant aged nineteen months in which such a murmur was present.

Looft reports a series of fifteen cases, ranging in age from three months to two and one-half years, only three being more than two years of age, in which such murmurs were present.

Rudolf found functional murmurs in 60 per cent. of the inmates of the Sick Children's Hospital in Toronto, while Butler found accidental systolic murmurs in 31.6 per cent. of a series of children between the ages of seven years and puberty. Sansom refers to the existence of these murmurs in early childhood. Weill holds the same views as Hochsinger as to their frequency.

Steffen considers accidental murmurs of more common occurrence under four years of age than is ordinarily believed.

Comby has found hemic murmurs at the base of the heart and in the vessels of the neck many times in anemic rachitic children.

Marfan thinks that anemia in young infants does not produce cardiac or vascular murmurs as frequently as in the adult, and he believes them very exceptional before the age of three years. He reports a case occurring in a boy, aged twenty-eight months, with symptoms of cardiac disease. The murmur was soft and systolic in time. The patient died and nothing abnormal was found in the heart.

Thiemisch reports a somewhat similar murmur in an infant aged six months. The autopsy revealed no abnormalities in the heart.

Drummond says that "cardiohemic" or "anemic" murmurs are quite common in children who are below par from any cause, especially when they are examined in the recumbent posture.

Practically all the authorities we have quoted admit the occurrence and comparative frequency in later childhood of functional murmurs of the type we describe, but we desire again to emphasize the fact that the vast majority, and especially the authors of text-books on pediatrics, consider accidental, anemic, or functional murmurs extremely uncommon prior to the fourth year.

In our former communication we had made no studies which gave us a very clear appreciation of the frequency of the inorganic late-systolic pulmonary murmur in infancy and childhood. We saw it often enough to make us realize that it is extremely common, and, in a study of a series of thirty-four consecutive cases in St. Vincent's Home, of infants ranging in age from two weeks to three and one-half years, we found it present in 21, or 61.7 per cent., distributed as follows: Eight times in nineteen children under one year of age; twelve times in fifteen children between one and three years of age; and in one child three and one-half years of age it was also present.

In order to obtain some additional evidence as to its actual frequency, we have studied forty-six children in the Southern Home for Destitute Children, ranging in age from three to ten years.

Of the five aged three years, four had the murmur; of the nine aged four years, seven; of the five aged five years, three; one of the five aged six years had an organic lesion and the four remaining had the functional murmur; five of the six aged seven years had it; three of the four aged nine years and only two of the five aged ten years.

It is seen, therefore, that of the total number (forty-six), thirty-two or 69.5 per cent. showed the presence of murmurs; and that of the fourteen under five years, eleven, or 78.5 per cent., had murmurs; while of the thirty-two between the ages of five and ten years, murmurs were present in twenty one, or 65.3 per cent.

Adding together the number of children examined consecutively in the preparation of our former paper and the forty-six examined consecutively in the preparation of this paper, we have a total of eighty of which number, fifty-three or 66.2 per cent. showed the murmur. Of these eighty children forty-eight were under five years of age, and of this number, thirty-two, or 66.2 per cent. had the murmur. Of the thirty-two remaining, all of whom were over five years of age, there were twenty-one, or 65.3 per cent., with the murmur. On the basis of these figures, therefore, it would seem that in institutional children, showing no special manifestations of disease, acute or chronic, but influenced only by their environment, between 60 and 70 per cent. have the type of murmur under discussion, and that this murmur is quite as common in children under five years of age as in later childhood. It is interesting to note also that these results correspond closely with those obtained by Rudolf, quoted above, and that the 31.6 per cent. of functional murmurs found by Butler in the examination of a series of hearts in children ranging in age from seven years to puberty would seem to support the suspicion suggested by our figures—that this murmur is more common during the first five years of life than between this age and puberty—a view which we have held for some years.

While this murmur is doubtless more common in children living in an environment such as obtains in institutions of the class we have worked in, we are, nevertheless, convinced from our experience in private practice among the better class of people that it occurs with almost equal frequency in children living under the best hygienic conditions, who have practically no evidences of anemia, and whose state of health is very slightly below the normal, and not infrequently in those who have every appearance of being perfectly well. Of course, they are much multiplied in frequency during the acute febrile conditions, or during any decided condition of ill health.

This murmur has no special clinical significance. The recognition of the frequency of its occurrence is important in order that it may be differentiated from murmurs of organic origin.

If its characteristics are fairly understood, it is not likely that it will be misinterpreted The points upon which one should

lay special stress in differentiating it from organic murmurs are these:

The changes in the heart muscle found in organic disease of the heart, as indicated by displacement of the apex-beat and increase in the area of dulness, are not present. The murmur is proportionately more augmented by the recumbent posture than are the organic murmurs; it is often audible only when the patient is recumbent. It is differently influenced by respiration, being loudest at the end of expiration and the beginning of inspiration, sometimes entirely disappearing at the end of a full inspiration. The murmur invariably has its point of maximum intensity in the second left interspace close to the sternum or over the third costal cartilage. It is sometimes transmitted over practically the entire cardiac area, but rarely beyond it. It never eliminates the first sound, but exists only after the period of systolic closure; it is, in other words, late-systolic.

PAROXYSMAL IRREGULARITY OF THE HEART AND AURICULAR FIBRILLATION.

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The following case of marked irregularity of the heart occurred in the service of Dr. Peterson, professor of gynecology and obstetrics in the University of Michigan. Careful examination of the heart was made and a number of sphygmographic tracings were obtained. Unfortunately at that time we were not acquainted with Mackenzie's methods of taking the venous and liver pulses and failed to take advantage of this most valuable method of analyzing cardiac irregularity. The case is of considerable interest, however, and the light which seems to be thrown on it by our experience of irregularity in animal experiments encourages us to put it on record. The history of the case as supplied by Dr. Peterson is as follows:

Mrs. H. H., a widow, aged sixty-four years, was admitted to hospital, December 23, 1901, for ovarian fibroid. She was operated on December 24. Anesthesia (ether) for one hour and twenty minutes. Her condition was good at end of the operation; pulse 90. Nausea persisted throughout the 24th, and on 26th the patient vomiting repeatedly, but on the 27th some improvement was noted in this respect. The pulse on the 25th and 26th was 90 to 100 at

the visiting hours, but the nurse stated subsequently that she had noted frequent irregularities.

On the 27th the pulse was 88[1] at 6 A.M.; 57 at 8; 53 at 10; 86 at noon; 51 at 2 P.M.; 92 at 4; 86 at 6; 52 at 8; 82 at 10; and 54 at midnight. At 2 P.M. the record states "pulse very irregular." Temperature 98° to 99°.

December 28. Slight nausea, and vomiting occasionally. Pulse weak and irregular. Sphygmograms taken in the afternoon indicate the same irregularities as occurred on the 29th. The attacks of irregularity did not last long. Strychnine $\frac{1}{30}$ grain, every four hours.

December 29, 8.30. Pulse very irregular, but regular at 9:15. In the afternoon pulse tracings were taken every hour, showing the following conditions: At 1.45 great arrhythmia; 2.45 pulse regular; 3.45 irregular again; 4.45 irregular and this persisted through the rest of the day.

On December 30 nausea and vomiting stopped, and subsequently there was general improvement. The periods of irregularity became less frequent and were confined almost entirely to the night. The patient says she wakes up with a start and the heart becomes very irregular at once.

On January 11, 1902, the heart was very irregular during the night, but afterward remained regular until January 18, when she was discharged from the hospital and reached home in the evening. The patient reported that her heart was very irregular during the following night.

The patient gives the following history of the trouble with her heart: She first noted the irregularity twenty years before, during an illness, and since then it has occurred whenever she was ill, excited, or exhausted. Vomiting, to which she is occasionally subject, has always been followed by heart irregularity. The tendency to irregularity seemed to increase about ten years before the operation, as she observed that less important occasions gave rise to it than previously. A letter received from the patient in 1905 states that for two years after the operation she suffered very little from her heart, but then some overexertion gave rise to cardiac irregularity again, and for the last year very slight exertion or exposure to extreme heat or cold has induced an attack.

The examination of the heart by the usual clinical methods during the stay of the patient in the hospital gave no clue to the cause of the irregularity. No enlargement of the cardiac dulness could be made out, there were no murmurs, and no objective signs of heart failure apart from the irregularity were present.

[1] We attach no importance to these numbers as indicating the true rate of the heart, as it is quite impossible to determine the pulse-rate in the type of irregularity shown in the sphygmograms. The numbers given, however, indicate periods of irregularity at 8 A.M., 2 P.M., 8 P.M., and midnight, while the intervening counts indicate a return to the normal.

ANALYSIS OF THE SPHYGMOGRAMS. The pulse tracings were taken with Jacquet's sphygmochronograph, recording one-fifth seconds. The tracings obtained during the irregular periods were all of the same type and may be represented by some of those taken on December 29. The marker above the tracing records the time

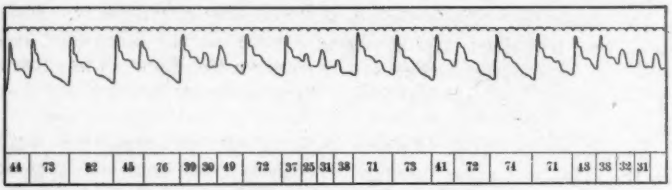

FIG 1.—Pulse tracing at 1.45 P.M. December 29.

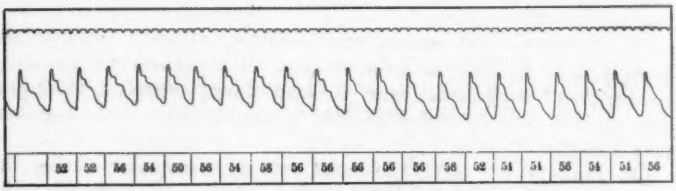

FIG. 2.—Pulse tracing at 2.45 P.M. December 29.

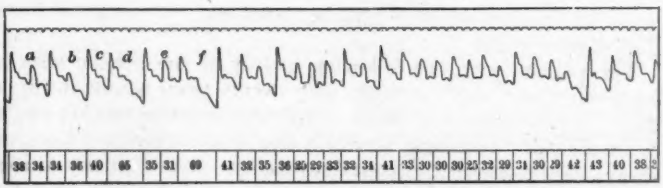

FIG. 3.—Pulse tracing at 3.45 P.M. December 29.

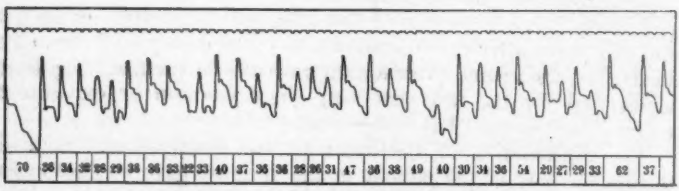

FIG. 4.—Pulse tracing at 4.45 P.M. December 29.

in one-fifth seconds, while the intervals between successive pulses are given below in hundredths of a second.

Of these four tracings, those taken at 1.45, 3.45, and 4.45 P.M. indicate marked and continuous irregularity, while the intervening one at 2.45 presents a quite satisfactory regular pulse of about 88

per minute. This rate is considerably above the average for the age of the patient, but is not to be considered as abnormal.[2] The slight variations in the intervals between the pulsations are not greater than those observed in normal persons. Auscultation at this time indicated no abnormality in the heart sounds; in short, the heart and circulation at this time appeared normal.

The tracings taken before and after this period of regularity offer a marked contrast, the pulse showing great variations in the strength of the beats. The general character of the tracings shows a number of large pulsations occurring at irregular intervals and having interspersed among them smaller pulsations, sometimes singly, at other times in twos or threes, or in groups of larger numbers.

Examination shows that the large excursions of the lever are not so simple as they appear at first sight. For example, in Fig. 1 the descent following the second and third rise of the lever is interrupted by oscillations which are obviously due to a beat of the pulse in each case too weak to make a more definite record. This is perhaps better shown in Fig. 3, in which at *a* and *b* the large excursion of the lever is followed by a weaker contraction, while at *d* the descent of the lever shows only a slight oscillation; yet there can be no question that there was here a secondary contraction similar in character to those at *a* and *b*, but so weak that it failed to cause even such a beat as is recorded at *b*. In the interval *c*, on the other hand, there was probably no interposed systole of the ventricle. When the stethoscope was applied over the heart there was found a duplication of the first sound in such intervals as have been recorded at *a*, *b*, and *d*, while there was no such duplication at *c*. At *e*, Fig. 3, two small elevations followed each other, and at *f*, a third one occurred which was too feeble to do more than arrest the fall of the lever for a moment. A little later, in Fig. 3, a succession of eleven rapid weak contractions are seen. Counting these weak and almost unrecorded contractions, the pulse is found to be beating in the irregular periods at 140 to 150 a minute. On auscultation the heart sounds were found to be very much more rapid than the pulse taken by the finger, which was given as about fifty a minute during the irregular periods.

Even when these small beats were taken into account the rhythm of the heart is very irregular; for example, during a succession of rapid contractions in Fig. 3, the interval between the successive pulses varies from 0.25 to 0.41 second. There exists no such "regular irregularity" as has been described under the terms pulsus bigeminus or trigeminus. In these, one normal pulsation is followed regularly by one or two movements of smaller dimensions, but in our tracings no such sequence is to be made out.

[2] Mackenzie, The Study of the Pulse, p. 53.

Even more striking than the irregularity in the pulse rhythm in this case is the marked variation in the strength of the beats. This variation in strength is, of course, a very common phenomenon in irregularity of the heart. In the numerous tracings published of late years by Wenckebach, Mackenzie, Cushny, and others, this variation in strength is universally noted. But in most of these the strength of the beat varies with the length of the preceding interval; the ventricle accumulates more energy during a long interval and at the same time receives more blood from the auricle, and these two factors together cause a very powerful contraction and a very large output of blood. In this case, however, the size of the pulse bears no relation to the length of the preceding interval. It is true that when there has been a great fall in the pressure from the absence or inefficiency of the preceding beat, the next contraction is often very large; but this is obviously not the determining factor in most instances, for a strong contraction is often preceded by a shorter interval than a smaller one, and in other cases two intervals of equal length are followed by pulsations of very different height. The variations in the size of the pulse must be due, therefore, not to different degrees of recuperation in the contracting power of the ventricle, but rather to variations in the amount of blood which it receives from the auricle during its diastole. The amount of blood entering the ventricle may be altered by a variety of causes. One condition which usually causes pulses of different sizes is the beating of the ventricle and auricle at different rates. For example, if the auricle beats three times to the ventricle's twice, one of the auricular beats discharges no blood into the ventricle, because the auricle contracts against the contracted ventricle. The next pulse is correspondingly small. This condition, however, leads to a rhythmical variation in the strength of the pulse, as has been shown by one of us in the case of certain poisons which lead to a ventricular rhythm independent of, and different from, that of the auricle.[3] No such rhythmical variation in the size of the pulse is to be made out in this case, so that the condition is obviously different from that occurring in animals under the influence of these poisons. An irregular and intermittent beat of the auricle might, however, cause the occasional discharge of blood into the ventricle during the diastole and thus lead to a large pulse-wave from the next ventricular contraction; the ventricle's rhythm must have been much more rapid than that of the auricle, and, of course, must have been developed independently.

Another factor which may determine the variations in the strength of the pulse in this case is the imperfect diastole of the ventricle. The blood can flow from the auricle only when the intra-auricular pressure is higher than the intraventricular, and if the ventricle

[3] Journal of Physiology, xxv. 49.

remains half-contracted during diastole, the inflow must be small and the next pulse correspondingly low. If this be the correct explanation of the variations in the size of the pulse, these are, of course, due to the ventricle alone. The auricle might be beating at the same rate as the ventricle, or it might be entirely inactive, the blood simply entering the ventricle from the auricle through the pressure exerted on it by the right heart.

From the evidence of the tracing we are unable to determine which of these two factors determine the size of the pulse. If the venous pulse had been registered simultaneously with the arterial, much light would have been thrown on the point, and it would probably have been possible to decide whether slow, intermittent, irregular contractions of the auricle are the explanations, or variations in the degree of relaxation of the ventricle. In the absence of such evidence the latter appears the preferable. It is a feature familiar to everyone who has watched an irregular heart in the living animal, while it is extremely rare to find the auricle beating so much more slowly than the ventricle, as would be indicated by the number of full pulses.

The regular beat of the ventricle which is registered by the sphygmograph in normal persons follows an impulse which originates in the "rhythmic area" around the great veins of the heart and is propagated to the ventricle by way of the auricle. Two factors are thus involved directly: (1) The discharge of the impulse from the rhythmic area must be regular and its path through the auricle unobstructed; and (2) the ventricle must always be in such a condition that it can respond to the stimulus, while its irritability is too low to permit of its initiating a contraction spontaneously. Irregularity of the heart arises either from irregularity in the discharge of the impulses or from an abnormal condition of the ventricle, which leads to spontaneous contraction before the descending impulse reaches it; in rarer cases the ventricle is unable to respond to the descending impulse and a beat lapses. Careful examination of the pulse often determines whether the irregularity arises from ventricular disability or from the irregular action of the originating area.[4] In an intermittent pulse due to ventricular lesion the intermission is almost exactly twice the interval between two normal beats, while if the discharging area be at fault the intermission is considerably shorter. The fact that the intermission due to ventricular abnormality must be a multiple of the normal length of the pulse wave, follows directly from the consideration that the impulses descending through the auricle are undisturbed in rhythm, and the intermission can end only on one of these reaching the ventricle and originating the first normal beat after the irregularity. That the intermission

[4] Cushny, Journal of Experimental Medicine, iv, 327; Mackenzie, loc. cit., p. 297; Wenckebach, Ztschr. f. klin. Med., 1899, xxxvi, 181, and Die Arythmie des Herzens, Leipsig, 1903.

is shorter when it is due to an irregular discharge from the rhythm-giving area was first deduced from animal experiments and has been found to conform with clinical experience in too many cases to permit of further doubt.

In our case of irregularity there is no reason to suppose that the ventricle failed to respond to the impulses it received. The length of the apparent intermissions or of the periods of short and quick pulses is not a multiple of the single beats. For example, in Fig. 1 the first single beat is 0.44 second in duration, and if the next intermission had been due to the failure of the ventricle to contract on the next regular stimulus its length would have been 88 instead of 73. Similar reasoning in each case shows that the irregularity is due, not to variations in the ventricular receptivity of stimuli, but to an irregular discharge of impulses or to an irregular transmission through the auricle or auriculoventricular fibers.

The question arises whether these irregular impulses originate from the same point as those in the normal regular pulse, or whether the irregularity of the discharge is due to the fact that some other point takes up the function, and, being only imperfectly adapted to it, issues only irregular impulses. The latter view has been suggested by Mackenzie,[5] who holds that in certain forms of continued irregularity the ventricle assumes an automatic or endogenous rhythm, while the auricle may assume the ventricular rhythm or may remain quiescent or "paralyzed." Mackenzie supports this view by a careful analysis of his tracings and by excluding all other known factors; in the particular cases observed the interpretation may be correct, although the argument by exclusion of all known causes is dangerous and an alternative explanation might possibly suffice without the necessity of adopting the inversion of the cardiac rhythm postulated by him. But in animal experiments in which the ventricle has been induced to take up an endogenous rhythm by means of drugs no such irregularities of the heart rhythm are observed,[6] and in numerous unpublished experiments in which rapid induced shocks were applied to the ventricle, one of us was able to invert the cardiac rhythm, the ventricle giving the rhythm to the auricle, without rendering the rhythm of either irregular after the first few seconds. An endogenous ventricular rhythm may, therefore, be perfectly regular in the mammalian heart, and it cannot be assumed *per se* to be the explanation of irregularity in the tracings under discussion.

In our tracings, then, there is nothing to suggest that the ventricle originated the rhythm anywhere. Although we cannot exclude the possibility of the whole phenomenon being due to endogenous ventricular influence, it seems rather to have merely responded to

[5] Study of the Pulse, Brit. Med. Jour., March 5, 1904.
[6] Cushny, Jour. of Physiology, xxv, 49.

the impulses which it received at irregular intervals from the auricle. Not infrequently the impulses followed each other so rapidly that the ventricle could not dilate sufficiently in the interval to permit of the entrance of blood from the auricle. In other cases blood failed to enter in quantity, although there seemed to have been sufficient interval, and in this case the ventricular contraction caused a very small pulse wave.

The conditions of the auricle and rhythmical area in the irregular periods appear to have been one of extreme activity, if, as we believe, the rhythm in this case was given to the ventricle by some other part of the heart. This impulse-emitting area was obviously in a state of great irritability, for the impulses amounted to 150 a minute, and at the same time the rhythm was extremely irregular.

The sudden onset of irregularity and its temporary character suggest that while there may be cardiac conditions favoring irregularity, the actual change from the regular beat must be due to affection of other organs. And the fact that it accompanied the nausea and vomiting and tended to occur when no exertion had been made, and especially in the night-time, suggest that the immediate cause of the irregularity was some abnormality of the central nervous system acting on a damaged heart. We are aware that the tendency at present is to regard such conditions as of peripheral origin and to exempt the central nervous system from responsibility in such phenomena. At the same time, the history of the case inevitably suggests this view, and we hope in the following pages to show indisputably that the central nervous system is capable of giving rise to very marked abnormalities of the heart action.

ANIMAL EXPERIMENTS.

In the course of the long series of experiments and demonstrations on the dog's heart carried out in the pharmacological laboratory of the University of Michigan, during the last ten years, it has happened occasionally that on opening the chest the heart was found to be beating very rapidly and irregularly. Doubtless other workers in this field may have had similar unfortunate experiences, but we are unaware of any recorded cases. Our dogs were anesthetized with morphine, 0.2 to 0.3 gram hypodermically, and chloretone administered by the stomach tube. The operation consisted in performing tracheotomy, prolonging the median incision to the lower end of the sternum, sawing through the sternum along its whole length, and hooking the two sides of the chest apart, thus exposing the pericardium, which was opened. The myocardiograph was then applied to the ventricle and auricle and tracings taken on a kymograph with smoked paper. The anesthesia was invariably deep enough to prevent any manifesta-

tion of pain and the eyelid reflex was absent before the incision was made. Sometimes, however, spontaneous respiratory movements returned while the sternum was being cut through, or if these were present before they became quickened and deepened. It was soon noted that when this change occurred, the tendency to cardiac irregularity was much greater than in those experiments in which more profound anesthesia had been induced. Attempts were made to record the changes in the pulse during the operation, but in the experiments in which this was done the irregularity was not developed. In several cases, however, it was noted that the heart rhythm was normal before and during the first part of the operation, but that when respiratory movements were induced by cutting through the sternum, the pulse, which had previously been of the usual slow vagus type seen in the dog, suddenly became accelerated and irregular. On examination of the heart in these cases, before the apparatus was applied to it, the ventricles were found in rapid irregular movement; the relaxation was often very imperfect between three or four successive contractions and then more complete for one or two beats. The impression was given that the ventricles were responding to a series of very rapid impulses which prevented their diastole, and that they could only relax when their irritability was reduced by fatigue, and then the more complete diastole followed. The auricles were widely dilated and no systole occurred in them; they were not wholly paralyzed and inactive, however, for on close inspection the fibers proved to be in a state of continual inco-ordinated contraction, each part of the auricle undergoing continuous fibrillary contraction independent of all other parts. The heart was in fact in the condition known to physiologists as auricular delirium, or fibrillary contraction in the auricle.

Auricular delirium is not infrequently produced by poisonous doses of bodies of the digitalis series,[7] and is very readily induced by rapid induction shocks passed through the auricular walls in animals. Several papers[8] dealing with the subject have appeared recently from the laboratories of Berne and Brussels, and we have also devoted some attention to it. In this condition the ventricle beats much more rapidly than normally and the beats are irregular in rhythm and vary in the degree of systole and diastole. Stimulation of the vagus, in our experience, which coincides with that of Kronecker and Spallitta, has no effect whatever on the movements of the auricle, while the ventricle is rendered slower and more regular or may be arrested completely. Phillips believes that the fibrillation of the auricle is lessened by stimulation of the vagus. It may be mentioned that the tremor in the tracing of the auricle

[7] Cushny, Journal of Exp. Med., ii, 233.

[8] Kronecker and Spallitta, Arch. Internat. de physiologie, ii, p 223; Philips, ibid., ii, p. 271; Fredericq, ibid., ii, p. 281.

during delirium often appears less marked, but this is due to the fact that the ventricle is slower and communicates less movement to the auricle, the fibrillation of the auricle causing no movement of the lever in itself. The more regular contraction of the ventricle under vagus stimulation is obviously due to the fact that the impulses from the auricle pass less rapidly through the block; when they are altogether excluded by section of the auriculoventricular band the ventricle beats regularly (Fredericq). The pulse, as well

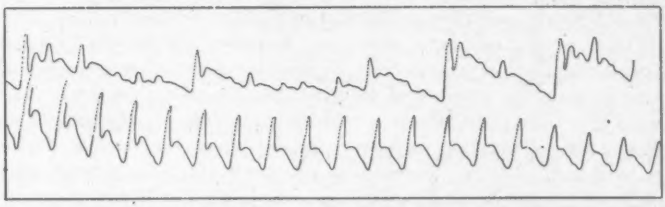

FIG. 5.—Pulse tracing from dog's carotid taken with Hurthle's tonometer. The lower tracing is normal; the upper was taken during auricular fibrillation from rapid electrical stimulation of the auricle.

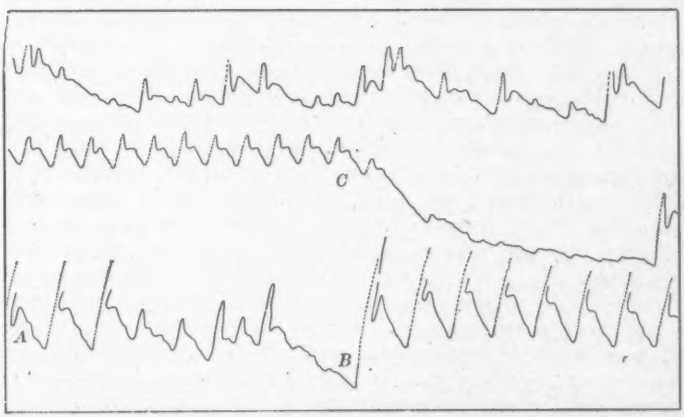

FIG. 6.—Pulse tracing from dog's carotid taken during auricular fibrillation, as in Fig. 5. At *A* feeble electrical stimulation of the auricle caused slight irregularity; *B*, stimulation discontinued and heart returned to normal; *C*, the heart previously normal received rapid electrical shocks in the right auricle which began to fibrillate; the uppermost tracing was obtained during auricular fibrillation.

as the movements of the ventricle and auricle, were recorded by Phillips; during the auricular fibrillation the pulse was accelerated and very irregular, as we have also observed in our experiments.

Stimulation of the dog's auricle with rapid induced shocks causes fibrillary contractions which pass off when the current is shut off or very soon afterward. On repetition several times, the

interval between the cessation of stimulation and the return of the normal auricular contractions becomes longer until finally it may continue for an hour or more after the electrodes have been removed. Such cardiac depressants as chloroform have no remedial effect even when pushed until the ventricle almost ceases under them. The only way in which we have been able to restore the auricle to regular contraction in persistent fibrillation, and this is not successful except occasionally, is by the application of cold directly to the heart. Large quantities of chilled salt solution poured on the exposed heart sometimes restored it to regular contraction.

The auricular delirium, which we have described as occurring in dogs during the operation, was obviously the result of sensory stimuli carried from the chest wall to the central nervous system. This might affect the heart either by producing changes in the circulation (shock) or by nervous impulses passing along the cardiac nerves to the heart. In the descriptions of shock given in surgical textbooks, the heart is often said to be irregular, but personal inquiry among our surgical friends failed to elicit any information in regard to the character of the irregularities, and we were led to the conclusion that the cardiac irregularity in shock is extremely rare or only seen in moribund cases. We are, therefore, disposed to attribute the condition to reflex nervous influences. These impulses must reach the heart either by the vagus or by the sympathetic fibers. And as a matter of fact, we have observed one instance in which vagus stimulation was followed by delirium. In this dog the heart was peculiarly irritable and much accelerated. The myocardiograph had been attached to the right ventricle and auricle and a tracing was being taken. The effects of electrical stimulation of one vagus in the neck were being demonstrated and the usual response followed, arrest of the auricle and the ventricle in diastole. But when the current was shut off, the heart, instead of returning to its normal rate, passed into fibrillary contractions in both auricle and ventricle. This is the only instance in which we have seen the unpoisoned heart affected in this way from the cessation of inhibition. In several experiments in which the irritability of the heart was exaggerated by large doses of the members of the digitalis series or of barium, section of the vagus led immediately to fibrillary contractions in the auricle and ventricle.

As has been stated, we have obtained no tracings of the pulse in dogs in which the heart passed into auricular delirium during the operations. The phenomenon is a rare one in our experience, although we have observed it sufficiently often to have no doubt as to its occurrence and as to its association with the operation. In several experiments the pulse was recorded during the operation by means of von Frey's tonometer attached to the carotid artery and the anesthesia was maintained at a point at which, while

pain was absent, the reflexes were retained as far as possible. In none of these, however, was the auricular delirium developed, although the pulse was much accelerated; occasionally intermissions of the pulse occurred of the auricular type, indicating perhaps a tendency to fibrillation. The acceleration was very slight or entirely absent in experiments in which atropine had been previously injected in quantities sufficient to paralyze the cardiac vagus. The acceleration in dogs without atropine was due, therefore, for the most part to lessened vagus tone from the centre, being inhibited by impulses from the seat of the operation. It seems likely that the auricular delirium observed in rare cases in dogs during the operation is similarly to be explained by the disappearance of inhibition; the auricles in these cases, however, must be in some quite unusual condition of irritability.

Of course, we cannot claim to have shown any connection between this type of irregularity in the dog's heart and that in the case described. At the same time there exists similarities between them, and the sudden arrest of the irregularity in each suggests a common cause; in the dog the site of the lesion is the central nervous system, and the history of the patient suggests that here also the irregularity was of central origin. We had hoped to have the opportunity of continuing the investigation in other cases of irregular heart, but as circumstances preclude our working further together, we have decided to put the imperfect investigation on record, in the hope that others may be interested in the suggestion made and may be able to prove or disprove its correctness.

SUMMARY. A case of paroxysmal arrhythmia, with marked acceleration of the heart, is described, and it is shown that the irregularity is due to irregular discharge of impulses and not to defects in the contraction of the ventricle which appears to respond to the impulses received. A similar form of irregularity in the dog's heart is described, and it is shown that this is due to the ventricles receiving irregular stimuli from the auricle which is in the state of fibrillation. This form of arrhythmia is shown to occur in the dogs occasionally from peripheral irritation and it is probable that this gives rise to reflex inhibition of the vagus centre which, acting on an abnormal heart, causes auricular fibrillation. The suggestion is made that in the patient described and in other cases of paroxysmal arrhythmia the condition is due to auricular fibrillation from inhibition of the vagus centre.

HEMOCHROMATOSIS WITH DIABETES MELLITUS.[1]

By Thomas B. Futcher, M.B.,
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The clinical and pathological features of hemochromatosis were presented before this Association in 1899 by Dr. Opie,[2] who reported a fatal case of the disease. Opie's paper gives a complete bibliography of the subject up to the date of publication. At the same meeting, Dr. Osler exhibited a patient who showed some of the leading characteristics of the affection. This case was[3] later published in detail.

There are three cardinal symptoms manifested by hemochromatosis in its most advanced stages: (1) Pigmentation of the viscera, and usually also of the skin; (2) cirrhosis of the liver, almost invariably of the hypertrophic type and accompanied by striking pigmentation of the organ; and (3) diabetes mellitus, which dominates the clinical picture in the latest stage of the disease. The latter is due to the final development of a pigmentary cirrhosis of the pancreas, thus interfering with its glycolytic function.

In Opie's and Osler's cases the disease had not reached the diabetic stage. Death in Opie's case, was precipitated by an attack of typhoid fever. Osler's patient presented a striking pigmentation and had a very large liver. Efforts have been made to trace the course of the disease in the latter case, but the patient has been lost from view. I have the privilege[4] of reporting herewith two fatal cases of hemochromatosis from the medical wards of the Johns Hopkins Hospital, in which diabetes was present and was responsible for the death of the patients. The paper deals only with those cases of hemochromatosis in which the diabetic stage has been reached. In 1899 Anschütz,[5] including one of his own, collected twenty-four cases of hemochromatosis with diabetes. In a review of the literature since that date I have been able to find nine additional cases, which, with the two here reported, make a total of eleven cases reported since 1899. Altogether, therefore, thirty-five cases of hemochromatosis with diabetes have been recorded up to the present time.

Hemochromatosis is a rare disease. In the first seventeen years since the opening of the Johns Hopkins Hospital up to May 15,

[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

[2] Transactions of the Association of American Physicians, 1899, vol. xiv, p. 253. (For the literature previous to 1899 see the bibliography as given by Anschütz and Opie.)

[3] Brit. Med. Jour., 1899, vol. ii, p. 1597.

[4] I am indebted to Dr. L. F. Barker and Dr. W. S. Thayer for the opportunity of reporting these two cases.

[5] Deut. Arch. f. klin. Med., vol. lxii, p. 411.

1906, there have been only three cases in the medical wards and dispensary, in which, from the clinical features and the finding of hemosiderin in the skin, the diagnosis was without doubt. These cases include Osler's case and the two here reported out of a total of 106,000 medical cases treated in the wards and dispensary. As already stated, only two of these had reached the diabetic stage. That hemochromatosis is an uncommon cause of diabetes is indicated by the fact that it was responsible for the disease in only two instances out of a total of 256 cases of diabetes treated in the medical wards and medical dispensary up to May 15, 1906. The histories of these two cases follow:

CASE I. (*Gen. Hosp. No.* 46430).—*Moderate pigmentation of the face, neck, and hands. Iron demonstrated in the epithelial cells of the sweat glands. Very large liver. Time of onset of pigmentation uncertain. Death from coma twenty months after the onset of the diabetic symptoms.*

E. W. S., male, white, married, aged forty-five years, cigar manufacturer, a resident of Virginia, was admitted to the Johns Hopkins Hospital, April 21, 1904, complaining of "diabetes."

Family History. The only feature of interest was that one brother had died of diabetes at the age of forty-nine.

Personal History. The patient had measles and whooping-cough as a child. Since then the only serious illness was pneumonia at thirty-three. He had gonorrhœa at twenty-five. No lues. Smoked six to ten cigars a day. Previous to two years before admission he had been a heavy drinker, taking from ten to thirty drinks of whiskey daily. His average weight when he was well was 195 pounds.

Present Illness. In January, 1903, the patient began to have marked polyuria and thirst. This was accompanied by increasing weakness and emaciation. He had lost sixty-five pounds since January, 1904. His appetite was ravenous. For three months he had suffered from a general pruritus. Recently a papulosquamous eruption had appeared on the legs and thighs. During the last two months there had been severe cramps in the muscles of the legs. The sexual power had been markedly impaired for a year. Neither the patient nor his friends had been struck by any change in his color.

Physical Examination. The patient was of medium stature and still fairly well nourished. A feature that attracted one's attention at once was a definite but not extremely marked, slaty-brown pigmentation of the face, neck, and hands. The only other situation in which the pigmentation was increased was about the scrotum. In front of the right external malleolus there were three fading purpuric spots. There was no pigmentation of the sclerotics nor of the buccal mucous membrane. No jaundice.

The radial vessels were slightly thickened. The blood-pressure

was 123 mm. Hg. The pulse was otherwise normal. The breath possessed a faint, sweetish fruity odor.

The lungs showed signs of slight emphysema. The heart was normal.

The liver was markedly enlarged. The relative hepatic dulness commenced at the middle of the fourth interspace in the mammillary line. The absolute hepatic dulness began at the middle of the sixth rib and extended to a point in the mammillary line 5 cm. below the costal margin and in the median line to a point 14 cm. below the tip of the ensiform cartilage and only 3.5 cm. above the umbilicus. The left lobe of the liver was even more markedly enlarged, its edge disappearing beneath the left costal margin in the anterior axillary line. The edge of the liver was rounded and everywhere well felt. The liver surface was smooth.

The border of the spleen could not be felt. It appeared to be enlarged, however, as its percussion measurements were 10 x 22 cm.

The abdomen revealed a distinct fulness corresponding to the enlarged liver. In the epigastrium there was a properitoneal hernia. There was nothing otherwise to be made out on abdominal palpation. Ascites did not exist.

The deep reflexes were markedly diminished but were still to be elicited. The superficial reflexes were normal.

The ophthalmoscopic examination made by Dr. Mills showed no changes in the fundi.

Blood Count. Red cells 4,800,000 per c.mm.; leukocytes, 7700 per c.mm.; hemoglobin 87 per cent. An examination of a fresh specimen failed to show any evidences of lipemia.

Frequent examination of the stools revealed no excess of fat. Toward the latter part of his stay in the hospital, the patient had an annoying diarrhœa, having from five to ten loose movements daily.

Histological Examination of the Skin. Sections were made by Dr. Opie of a piece of pigmented skin removed from the back of one of the hands, and a marked reaction for iron was found in the epithelial cells of the sweat glands by the potassium ferrocyanide and hydrochloric acid method.

Summary of Urine Examinations. The total amount of urine for the first full twenty-four hours (April 22 to April 23) was 3200 c.c. The urine was clear and of a very pale yellow color. Acid reaction; specific gravity, 1033. No albumin. Sugar, 7 per cent., or 224 grams in the twenty-four hours. There were definite reactions for acetone and diacetic acid, although they were not intense. The microscopic examination was negative.

The patient was put on a non-carbohydrate diet by gradual withdrawal of the starches. After being on a strict diet for nine days he failed to become aglycosuric and was still excreting on the ninth day 75 grams of glucose. As he was losing weight, moderate amounts of starch were allowed. The reactions for acetone and

diacetic acid remained positive throughout the patient's entire stay in the hospital.

On May 12, the day before he left the hospital, he voided 1800 c.c. of urine. It was acid; specific gravity 1029; no albumin; sugar, 3.1 per cent. or 55.8 grams; acetone and diacetic acid positive; no casts.

The patient was discharged on May 13, 1904. His condition had not materially changed. The pigmentation had apparently remained about the same. The enlargement of the liver persisted. A clinical diagnosis of hemochromatosis and diabetes mellitus was made.

Dr. J. H. Neff, of Harrisonburg, Va., who had charge of the patient after he returned home, informed me that during the summer a superficial ulcer developed on one of the legs. This slowly healed. There was no special increase in the degree of pigmentation. The patient's condition gradually became worse and he died in coma on September 6, 1904, twenty months after the onset of his diabetic symptoms. Unfortunately no autopsy was obtained.

CASE II. (*Gen. Hosp. Nos.* 52486, *and* 53388).—*Intense pigmentation of many years' standing. Iron demonstrated in the cells of the sweat glands. Enormous liver. Symptoms of diabetes for six months before death. Death from bronchopneumonia and not from coma.*

J. W. S., male, white, married, bricklayer, aged fifty-three years, was admitted to the Johns Hopkins Hospital for the first time on October 6, 1905, complaining of weakness, thirst, and frequent micturition.

Family History. There was nothing of importance bearing on the patient's case.

Personal History. The patient had always been a very healthy man with the exception of an attack of pneumonia seventeen years ago. He denied gonorrhœa and syphilis. He had smoked and chewed tobacco in moderation. Alcohol was used very moderately, three glasses of beer a week. He was the father of eight children. His average weight was 160 pounds.

Present Illness. Six weeks before admission the patient first noticed that he was voiding urine more frequently and in larger amounts, and that he had persistent thirst. These symptoms were preceded for a short time by increasing weakness. During the last four weeks he had lost twenty pounds. His appetite had not been voracious. The bowels were constipated. Six days before admission he had to give up work owing to the increasing physical weakness. For three days he had noticed a diffuse, red eruption over the lower part of the chest, the abdomen, and genitals.

The patient had not noticed any recent change in his color. His daughter said that his skin had been dark for many years and as long as she could remember.

Physical Examination. The patient was fairly well nourished, his weight on admission being 132 pounds. The mucous membranes were of good color. One was immediately struck by the remarkable pigmentation of the skin. This was most marked over the face, neck, and hands, where the skin had a very dark-brown color. The skin of the whole body was much more pigmented than normal, and there was intensification of the color in the axillæ. Over both axillary regions, the lumbar regions of the abdomen, and the groins there was a bright erythema which disappeared on pressure. There was no pigmentation of the sclerotics nor of the buccal mucous membrane. Below the left eye there was a xanthoma plaque measuring about 3 mm. in diameter.

The radial vessels were moderately sclerosed.

The examination of the heart and lungs revealed nothing abnormal.

The liver was enormously enlarged. The relative hepatic dulness commenced at the level of the fourth rib in the mammillary line. The absolute hepatic dulness began at the fifth rib and extended to a point 12.5 cm. below the costal margin in the mammillary line, which was 2 cm. below the level of the umbilicus. In the median line the absolute dulness reached just to the level of the umbilicus. The left lobe was markedly enlarged. The edge of the liver was everywhere readily felt and somewhat rounded. The surface was smooth. The edge of the spleen was easily palpable at the costal margin on deep inspiration. The examination of the abdomen was otherwise negative. There was no ascites.

Both knee-jerks were present but slightly diminished.

Blood Examination. Red cells, 5,304,000 per c.mm.; leukocytes, 9200 per c.mm. Hemoglobin, 95 per cent. (Gowers). The differential count showed no special variations from the normal. There were no evidences of lipemia by either chemical or microscopic tests. On October 9, Dr. Walter Jones examined the blood spectroscopically and reported that only the normal bands of oxyhemoglobin were present.

Microscopic Examination of the Skin. On October 21, a small portion of the skin from the left shoulder was excised to be examined microscopically for iron. The examination was made by Dr. Bunting, who reported as follows: In the Malpighian layer of the epidermis the cells show an excess of fine pigment granules which do not take the Prussian-blue color with the ferrocyanide test. In some of the epithelial cells of the sweat glands and ducts, however, there are present coarser, more refractile granules, which do stain a brilliant greenish-blue and which are granules of hemosiderin. There were no large vessels found giving smooth muscle in which to look for hemofuscin.

Summary of Urine Examinations. For the first full twenty-four hours (October 7 to October 8) 1240 c.c. of urine was voided. It

was of amber yellow color; acid; 1034; no albumin; sugar, 4.8 per cent., or 59.5 grams in twenty-four hours; acetone and diacetic acid were present; no casts.

Throughout the patient's stay in the hospital sugar was constantly present, the largest excretion being 272 grams during the twenty-four hours on a mixed diet. The lowest excretion of sugar on a strict non-carbohydrate diet was 39 grams. He failed to become aglycosuric on October 21, when a "hunger-day" was instituted, 23 grams of sugar being excreted. Acetone and diacetic acid persisted in the urine throughout his entire stay in the hospital.

In order to see whether the urine gave any indications of excessive blood destruction it was tested, on October 19, for hematoporphyrin, but the spectroscope failed to give the characteristic absorption bands.

On October 21 the patient was discharged. His general condition had materially improved during his stay in the hospital, and he gained one pound in weight.

Second Admission. The patient was readmitted to the hospital on January 9, 1906. His main symptoms in the interval were a "tired, sleepy feeling," great weakness across the small of the back, and some swelling of the ankles.

The examination of the liver, skin, and urine revealed practically the same features as on the first admission. The urine contained from 4 to 6 per cent. of sugar, and there were quite marked reactions for acetone and diacetic acid. He was discharged on January 13, feeling about the same as on admission.

Observation Outside the Hospital. After leaving the hospital, I was able to follow the course of the disease. The patient progressively failed. His main complaint was drowsiness and great weakness in the lumbar region. His disposition changed and he would at times have violent fits of anger. The reactions for acetone and diacetic acid became very intense and persisted for a long time, even with large doses of sodium bicarbonate. Small amounts of carbohydrates were permitted daily. During the night of February 11, he had a chill and the temperature rose to 100.2° F. The next day patches of bronchopneumonia were detected over the lower lobe of the left lung. Fearing the onset of coma the sodium bicarbonate was increased to 4 grams every two hours and the patient was put on a diet of eggs, with a quart of milk and a half-pint of cream daily.

On February 14, contrary to expectation, the reactions for acetone and diacetic acid had entirely disappeared. There was 2.4 per cent. of sugar present. The physical signs of bronchopneumonia were apparent. The pulse was 132 and much weaker. The respirations were 32 to the minute, but had no suggestion of an "air-hunger" type. Although the patient was dull this seemed to be due rather to his general weakness than to advancing coma. He died suddenly

at 12.10 A.M. on February 15. Every effort was made to secure an autopsy, but the patient's family refused permission.

It was most unfortunate that autopsies could not be obtained in these two cases. Both patients died after leaving the hospital. I fully appreciate the risk in making a diagnosis of hemochromatosis without the evidences afforded by an autopsy. Personally I am fully convinced that both were cases of diabetes due to hemochromatosis. Each possessed the triad of symptoms characteristic of hemochromatosis in its final stage: pigmentation of the skin, hypertrophic cirrhosis of the liver, and diabetes of a severe type. Even with this symptom-complex one would hesitate to make a diagnosis of hemochromatosis without the finding of iron in the skin. In both these cases, however, hemosiderin was demonstrated in the epithelial cells of the sweat glands, in the first case by Dr. Opie, and in the second case by Dr. Bunting. I have, therefore, little hesitation in placing these two cases on record as instances of diabetes due to hemochromatosis.

In neither case was there any demonstrable evidence of blood destruction. In each the blood count was practically normal. In Case II the blood was examined spectroscopically for abnormal absorption bands, and the urine by the same means for hematoporphyrin with negative results. The only evidence of possible blood or vascular changes was in Case I, in the existence of a few small purpuric spots about one of the ankles. In Case I it was impossible to determine the relationship of the time of the onset of the skin pigmentation to the liver changes and diabetes. In Case II, however, the pigmentation undoubtedly antedated the diabetic symptoms which had existed for only six months before death. The skin pigmentation, having existed for as long as members of his family could remember, presumably also antedated the hypertrophic cirrhosis of the liver.

Before preceding to a brief consideration of the pathogenesis of hemochromatosis, I shall give a very brief summary of the cases of this disease associated with diabetes mellitus that have been reported since the appearance of the paper by Anschütz in 1899. The names of the observers and a brief synopsis of the cases follow:

I. Henry W. Berg.[6] Female; aged forty-four years; pigmented skin; exophthalmic goitre; enlarged liver; diabetes. Patient alive when reported. Skin not examined for iron.

II. A. Murri.[7] Female, aged fifty-nine years; pigmentation of arms; pediculi present; liver and spleen not enlarged. Highest percentage of sugar 4.3. Patient discharged "well." Skin not examined for iron.

III. K. Ubert.[8] Male; physician; age not given; 7 per cent. of

[6] Med. Record, 1899, vol. lvi, p. 881.

[7] Wiener klinische Rundschau, vol. xv, p. 345.

[8] Dissertation. Ueber Hemochromatolyse mit Pankreasatrophie und Diabetes (Zurich) Affoltern, 1902, J. Weiss.

sugar; enlarged liver and spleen. Death from coma. Diagnosis confirmed at autopsy.

IV. R. Lepine.[9] Male; aged forty-five years; 71 grams sugar in twenty-four hours; diabetes lasted eight months; enlarged liver and spleen; diagnosis confirmed at autopsy.

V. J. W. Beattie.[10] Male; aged thirty-nine years; pigmentation of the skin, which was thought to have followed the diabetes; death from coma; pigmentary cirrhosis of the liver and pancreas found at autopsy.

VI. L. Margain.[11] Male; aged forty-seven years; pigmentation of skin; relationship of onset of pigmentation to onset of diabetes not determined; enlarged liver. Autopsy.

VII. Hess and Zurhelle.[12] Case I. Male; aged fifty-two years; pigmentation of skin; diabetes; autopsy, showing hypertrophic pigmentary cirrhosis of the liver and sclerosis of the pancreas with pigmentation.

VIII. Hess and Zurhelle.[13] Case II. Male; aged fifty-three years; marked alcoholic; pigmented skin; severe diabetes; autopsy, showing hypertrophic cirrhosis of the liver and a pigmented, firm pancreas.

IX. G. H. Moll van Charante.[14] Male; aged thirty-two years; skin pigmentation; enlarged liver; severe diabetes; death from coma; autopsy, showing general hemochromatosis.

In 1882, Hanot and Chauffard first described two cases of diabetes mellitus associated with hypertrophic cirrhosis of the liver and a bronze-like pigmentation of the skin. Four years later Lettuile reported two similar cases. In 1886, Hanot and Schachmann reported a fifth case. As all these cases agreed in that there was diabetes, a pigmentary hypertrophic cirrhosis of the liver, and, with the exception of Hanot and Schachmann's case, pigmentation also of the skin, the latter clinicians felt that they had established the existence of a new form of cirrhosis, *cirrhose pigmentaire diabètique*, as well as a new form of diabetes, *diabète bronzé*.

The majority of French clinicians have held that the diabetes is primary; that the diabetic alteration of the blood causes a destruction of the red cells, with the deposition of the blood pigment in the viscera and in the skin, giving rise to the so-called bronzed diabetes.

When von Recklinghausen, in 1899, described a general pigmentation of the viscera under the name of "hemochromatosis," it became at once apparent that this condition was closely related to bronzed diabetes. von Recklinghausen found that the tissues in

[9] Lyon médical, 1903, vol. c, pp. 593 and 652.
[10] Journ. of Path. and Bact., 1903–1904, vol. ix. p. 117.
[11] Revue de Médecine, 1905, vol. xxv, p. 214.
[12] Zeitschrift f. klinische Medisin, 1905, vol. lvii, p. 344.
[13] Ibid.
[14] Neiderl. Tijdschr. v. Geneeskunde, Amst., 1905, vol. xli, p. 1727.

hemochromatosis contained two varieties of pigment. One of these, "hemosiderin," contains iron, and possesses a brown color, and is thought to be derived from the hemoglobin of the blood. It is found in the cells of the lymphatic glands, liver, pancreas, and the sweat glands. The other, "hemofuscin," contains no iron, is finer, of an ochre-yellow color, and is present in the smooth muscle cells of the stomach, intestines, bloodvessels, and lymphvessels, but rarely in those of the urinary bladder, ureter, and vas deferens. It is also found in the connective-tissue cells of certain localities—for example, Glisson's capsule, the trabeculæ of the spleen, and the sheaths of the bloodvessels.

As more cases of hemochromatosis were studied, the view gained ground that in this condition some unknown agent caused an increased vulnerability of the red cells with dissolution of the hemoglobin and deposition of the two pigments in the situations already noted. The deposition of the hemosiderin in the cells of the liver and pancreas and of the hemofuscin in the connective tissue of these glands eventually leads to the large, cirrhotic, pigmented liver and the sclerotic pigmented pancreas which are so characteristic of the disease. The general belief now is that diabetes develops in hemochromatosis only when the pancreatic tissue becomes so seriously diseased that the islands of Langerhans are largely destroyed. The glycolytic ferment, which is supposed to be formed in these islands, is no longer produced and is not able to render active, according to Cohnheim, another ferment-like body produced in the muscles, a function which, according to this observer, is necessary for the proper utilization of the carbohydrates. Consequently, an accumulation of glucose results, a hyperglycemia occurs, and permanent diabetes ensues. The diabetes is of a severe grade and dominates the picture in the late stages of the disease. Acidosis is nearly always present and the majority of patients die of diabetic coma. Death usually occurs within one year after the onset of the diabetic symptoms, although it was deferred for twenty months in the first case here reported.

As to the relationship of the diabetes to the pigmentation the above view is the one generally held. The pigmentation of the viscera is primary and antedates the diabetes. The skin is not always pigmented in hemochromatosis. There may be visceral pigmentation long before there is any bronzing of the skin. The view formerly strongly supported by the French clinicians that the diabetes is primary and responsible for the pigmentation and visceral changes has now few adherents.

The basal cause of hemochromatosis still remains an unsolved problem. The view generally held is that some unknown toxic agent causes an increased hemocytolysis of the red cells. In a few of the reported cases there has been some evidence to support this view, such as the rare occurrence of purpura and the existence of

hemoglobinuria in Case II of Hess and Zurhelle. On the other hand, Meltzer[15] has suggested that the absence of any anemia in these cases is strongly against the view that there is increased blood destruction in hemochromatosis. In a discussion of Berg's case he cites the fact that there is an absence of general hemochromatosis in pernicious anemia, in which there is increased blood destruction, as an argument against the view that hemochromatosis is due to a pathological condition of the red cells. He is inclined to think that the excess of iron in the tissues is due to a disturbance of the mechanism of metabolism which has to do with the removal of iron from the system. In other words, there may be an iron retention. As the amount of iron eliminated in the feces about equals that absorbed by the system from the food, he thinks that some light may be thrown on the subject by a quantitative analysis of the iron excreted in the stools.

The most thorough pathological and chemical study of hemochromatosis in recent years is that by Hess and Zurhelle. They strongly support the view that the cirrhosis of the liver and the pigmentation of the tissues are dependent on some common cause. They hold that some toxic substance, possibly alcohol, causes disturbances of metabolism which bring about both of the above changes. A lipemia, which was present in one of their cases, is explained in the same way. Their investigations also go to show that a sharp distinction between hemosiderin and hemofuscin cannot be made. They claim to have found them side by side in the same cell with gradual transitions from one to the other.

Of the thirty-five recorded cases of bronzed diabetes, including the two here reported, all but two were in males. These two have been reported since Anschütz's analysis of twenty-four cases in 1899, at which date he found that all the reported cases were in males. Cases in women have been reported by Berg, of New York, and Murri, of Bologno. The records of these cases, however, leave a doubt in one's mind as to whether they were true cases of bronzed diabetes. Neither came to autopsy and there is no report of iron having been examined for in the skin. It may be mentioned here that a case of hemochromatosis in a female was reported by Dr. Maude Abbott. As this patient did not have diabetes it has not been included in this series. The ages of the patients ranged from thirty to sixty years, with the exception of one patient who was sixty-one. The diabetes, as already stated, is the final stage of the disease and is in no special sense different from other cases of this affection. It is of a severe form and almost invariably causes death from coma within one year after its onset.

SUMMARY. Hemochromatosis with diabetes mellitus (bronzed diabetes) is a rare disease. Of 256 cases of diabetes, out of a total

[15] Medical Record, 1900, vol. lvii, p. 43.

of 106,000 medical admissions to the wards and dispensary of the Johns Hopkins Hospital, two were due to hemochromatosis. Of thirty-five cases in the literature, including the two here reported, all but two were in males. With one exception the ages of the patient ranged from thirty to sixty years.

Hemochromatosis in its final stages presents a triad of symptoms: (1) Pigmentation of the viscera and, in the vast majority of cases, also of the skin; (2) hypertrophic cirrhosis of the liver—very occasionally atrophic cirrhosis; and (3) diabetes mellitus, a terminal feature, due to a sclerosis of the pancreas causing destruction of the islands of Langerhans and consequent interference with the secretion of the normal glycolytic ferment.

Death usually occurs within a year after the onset of the diabetic symptoms, although it was delayed till twenty months in Case I, herewith reported.

The balance of opinion is in favor of the view that hemochromatosis is due to some toxic agent of unknown character and origin, which results in an increased destruction of the red blood cells with deposition of hemosiderin and hemofuscin in the body tissues. Whether the changes in the liver and pancreas are due to the deposition of the pigment or to the same toxic agent which is supposed to cause the blood destruction is still a disputed question. It has been suggested that the excessive amount of iron in the tissues may be due to defective elimination rather than to increased formation from the blood.

ACUTE PULMONARY ŒDEMA, WITH SPECIAL REFERENCE TO A RECURRENT FORM.[1]

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The œdema of the lungs to which I desire to call attention is not that so commonly seen in the period of lost compensation of valvular or muscular heart disease, in cachectic states, in grave infectious diseases, or in acute and chronic nephritis in the terminal phase. It bears no relation to subcutaneous dropsy, and in typical cases is not associated with it. In the suddenness of its onset, in the alarming character of its symptoms, and in the mortal peril in which it places the patient, acute pulmonary œdema resembles angina pectoris, and deserves, with equal propriety, a separate place in our text-books. Those who, interested in the subject, look through

[1] Read in abstract at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

the text-books and encyclopedias of medicine will be astonished to find how little mention is made of acute œdema of the lungs or, for that matter, of pulmonary œdema in general.

HISTORY. Laënnec,[2] in 1819, alluded in his chapter on œdema of the lungs to a suffocative orthopnœa that sometimes carries off children after an attack of measles, and considered it an idiopathic anasarca of the lungs.

Andral,[3] in his commentary to the fourth edition of Laënnec's *Traité de l'Auscultation médiate*, clearly describes acute pulmonary œdema, and compares it with œdema of the glottis; but neither in this commentary nor in his own *Cours de Pathologie interne*[4] does he speak of the causes. He recognizes three forms of œdema: (1) A fulminant form (forme suraigue), in which the patient is suddenly seized with an intense dyspnœa that in a short time causes death; (2) a subacute form, in which the dyspnœa, though sudden in onset, lasts somewhat longer before death ensues; and (3) chronic œdema, which does not concern us at the present time.

Legendre,[5] in 1846, speaks of an acute pulmonary œdema occurring during the course of scarlet fever.

Rokitansky,[6] like Andral, compares acute pulmonary œdema with œdema of the glottis; it is, he states, a frequent cause of suffocation in adults and newborn children, and is often combined with hyperemia and serous effusion within the cavity of the cranium.

Bernheim,[7] in his clinical lectures, refers to a fulminant pulmonary œdema during the course of acute articular rheumatism; and Lebreton,[8] among the pulmonary complications of rheumatism, mentions an acute œdema of the type under consideration.

Landouzy[9] observed two rheumatic patients with pulmonary œdema, one having four and the other five recurrent attacks; neither had albuminuria.

Jaccoud[10] reports a case of typhoid fever terminating fatally within fifteen minutes from acute pulmonary œdema, which he designates as "un veritable coup de sang pulmonaire." The autopsy revealed nothing to explain the tragic event.

Debove[11] speaks of repeated accesses of acute pulmonary œdema, and cites the case of a physician having aortic disease who died in half an hour in an attack, after having had several before. Debove thinks that aortic affections, and cardiac diseases in general, predispose to acute pulmonary œdema.

[2] Treatise on Diseases of the Chest and on Mediate Auscultation, 1830, p. 179.
[3] Laënnec's Traité de l'Auscultation médiate, 4ième édition, par Andral, t. xi, p. 424.
[4] Cours de Pathologie interne; 4ième édition, 1842, p. 123.
[5] Œdeme aigue du tissue cellulaire de poumon à la suite de la scarlatine, quoted by Fouineau.
[6] Manual of Pathological Anatomy, Sydenham Society's translation, iv, p. 71.
[7] Leçons de Clinique médicale, 1877, p. 494, quoted by Fouineau, q. v.
[8] Thèse de Paris, 1884, quoted by Fouineau.
[9] Bulletin médical, 1897, p. 445.
[10] Clinique de la Pitié, i, 1883, 1884, p. 567.
[11] Bulletin médical, 1897, xi, p. 400.

P. de La Harpe,[12] in 1881, reported three cases that illustrate the condition of acute pulmonary œdema very well: Case I. A woman, aged forty-three years, healthy, exposed herself to inclement weather after a slight attack of influenza; œdema of the lungs developed and caused her death within a short time. Case II. A woman, aged sixty years, also healthy, after one or two nocturnal attacks, died of œdema in a few minutes. Case III. A man had from fifteen to twenty attacks, all terminating by repeated eructations of gas and the voiding of large amounts of almost colorless urine. Similar cases are reported by Lund.[13]

One of the most important communications is that of Dr. Lindlay Steven,[14] of Glasgow, who, under the name of acute suffocative pulmonary œdema, reports two cases, in both of which there were evidences of renal disease; and in one of them there was also an affection of the aortic valve. Steven's paper stimulated the report of a number of other cases, one of the most interesting being that of Lissaman,[15] whose patient, a woman, aged forty-five years, had within two and a half years seventy-two attacks, all characterized by sudden onset, pain in the chest, frightful dyspnœa, lividity of the face, profuse cold sweats, labored action of the heart with small and rapid pulse, and the ejection, without cough, of enormous quantities of thin, pink, seromucous fluid. All the attacks were nocturnal.

Four well-studied cases have been reported by Hewlett,[16] who adopts Steven's designation of acute suffocative pulmonary œdema: Case I. A woman, aged forty-nine years, had six attacks—two in the afternoon, the others at night. Albuminuria, myocarditis, arteriosclerosis, and hypertension. Case II. A woman, aged fifty-two years, had repeated attacks, after each of which albumin and casts were present in the urine. In the intervals only casts were found. Heart hypertrophied; blood-pressure high. Case III. A woman, aged sixty-nine years, had ten attacks, all but one at night. Urine contained a trace of albumin; no casts. Case IV. An alcoholic woman, aged fifty-two years, who died in an attack of œdema.

A fairly typical case of the recurrent variety is reported in this country by Crummer.[17]

Among the most important systematic contributions to the subject from the clinical and pathological standpoint should be mentioned

[12] Rev. méd. de la Suisse Rom., 1881, p. 322.
[13] Lund. Norsk. Mag. for Lägevid, quoted by Huchard and by Fouineau.
[14] Lancet, January 11, 1902.
[15] Ibid., February 8, 1902.
[16] Intercolonial Medical Journal, 1903, p. 611.
[17] Northwestern Lancet, 1902, p. 203.

those of Huchard,[18] Dieulafoy,[19] Renaut,[20] Fuoineau,[21] Bouveret,[22] and Coplin.[23]

Its pathogenesis has been studied by Welch,[24] whose researches are of fundamental importance; by Sahli,[25] Grossman,[26] Löwit,[27] and others.

ETIOLOGY. Acute pulmonary œdema is associated with a variety of affections that, in a clinical sense, may be considered in the light of causes. I would classify them as follows: (1) Arteriosclerosis; (2) Bright's disease; (3) heart disease—angina pectoris; myocarditis; valvular affections; (4) asthma; (5) acute infectious diseases—typhoid fever, measles, rheumatic fever, influenza, pneumonia, etc.; (6) pregnancy; (7) paracentesis of thorax and of abdomen; (8) angioneurotic œdema; and (9) obscure conditions of questionable causal relationship (hysteria, etc.).

1. *Arteriosclerosis.* A large number of the reported cases of acute pulmonary œdema showed arterial disease. Case II of my series belongs to this group. Huchard[28] contends that vascular disease, especially aortitis and periaortitis, is the only cause of acute pulmonary œdema. No doubt it is an important factor in many cases, but not the essential one in all. Clifford Allbutt[29] admits the importance of aortitis; but very properly lays stress on the coexistence of general arteriosclerosis. The œdema results, according to Huchard, from disturbance in the innervation of the pulmonary vessels brought about by extension of the aortitic or periaortitic process to the cardiopulmonary plexus.

2. *Bright's Disease.* The important relationship that Bright's disease bears to acute pulmonary œdema was first clearly pointed out in 1890 by Bouveret, and afterward emphasized by Dieulafoy, Brouardel,[30] and others. Case I of my series is an illustration.

Dieulafoy, like Andral and Rokitansky, compares œdema of the lungs to œdema of the glottis, which is known to be one of the occasional complications of Bright's disease. How the nephritis acts has been much discussed by French writers: whether directly by toxemia (uremic poisoning) or indirectly through disease of the heart and aorta. For myself, I believe that nephritis can produce acute pulmonary œdema without the intervention of arterial or cardiac disease, through the mediation of poisons, the true nature of which remains unknown.

[18] Bulletin médicale, 1897, xi, p. 393.
[19] Bulletin médicale, 1897, xi, p. 400.
[20] Bull. de l'Acad. de Méd., 1897, xxxvii, p. 557.
[21] L'Oedème du Poumon, Thèse de Paris, 1898.
[22] Rev. de méd., March, 1890.
[23] Therapeutic Gazette, April, 1906.
[24] Arch. f. path. Anat. und Phys., 1878, lxxii, p. 375.
[25] Arch. f. exper. Path. und Pharm., 1885, xix, p. 435.
[26] Zeit. f. klin. Med., xii, xv, vxi, 1887–1890.
[27] Ziegler's Beiträge, xiv, p. 491; Centralblatt f. allgem. Path. und pathol. Anat., 1895.
[28] Loc. cit.
[29] Lancet, July 8, 1903, p. 141.
[30] Bull. de l'Acad. de Méd., 1897, xxxvii, p. 509: Bulletin médicale, 1897, xi, p. 400.

3. *Heart Disease.* I have separated this from arteriosclerosis, with which it is generally associated, because there are cases of œdema in the literature in which the last condition is not mentioned, and may be presumed not to have existed, but in which there was valvular disease of the heart. It must be remembered that the œdema here considered is to be distinguished, as I stated in the beginning of the paper, from the ordinary œdema of valvular disease, which is a part of a general œdematous process.

With regard to angina pectoris, the coincident occurrence of œdema is noted but by few authors. It is presented in Case V of my series. Angina pectoris is, no doubt, often associated with aortitis, but not necessarily so; and certainly not always with evident peripheral arterial disease. In my own case there was no general arteriosclerosis. I have for that reason separated the pulmonary œdema of angina pectoris from that of arteriosclerosis.

4. *Asthma.* The occurrence of acute suffocative œdema during the course of asthma is illustrated by two of my cases—III and IV. Differentiation of the condition from a violent asthmatic paroxysm can be made by attention to the physical signs, the character of the expectoration, and the profound collapse. Moreover, the patients themselves are aware that something very different from an asthmatic attack is taking place. It is quite probable that many of the so-called asthmatic attacks coming on in middle or advanced life, without any previous history of asthma, are in reality attacks of pulmonary œdema.

5. *Acute Infectious Diseases.* In the section on history I have already cited a number of authors who have observed acute pulmonary œdema during (*a*) typhoid fever (Jaccoud and Merklen[31]); (*b*) rheumatic fever (Lebreton and Landouzy); (*c*) scarlet fever (Legendre); (*d*) influenza (Glasgow[32] and Lemoine[33]); (*e*) pneumonia (Souin de la Savinière[34]).

6. *Pregnancy.* The first to report a case of acute pulmonary œdema during pregnancy was Charles Wilson[35] (1856), whose patient was a woman, aged thirty-four years, eight months pregnant. There was anasarca and scanty, high-colored urine (no analysis); sudden pulmonary œdema at night; recovery after abstraction of twenty ounces of blood. Premature, spontaneous labor, followed by puerperal mania, with recovery under opium.

Vinay,[36] in 1896, reported three cases of acute pulmonary œdema during pregnancy, two of which were speedily fatal; in all three there was mitral-valve disease, and in one of them also nephritis. One of my cases, VI, belongs to this group.

[31] La Méd. moderne, 1903, xiv, p. 145. [32] Amer. Jour. Med. Sci., April, 1895, p. 425.
[33] Press méd., 1905, p. 151.
[34] Contribution à l'etude de l'œdème aigue du poumon, Thèse de Paris, 1873, quoted by Fouineau.
[35] Edinburgh Med. Jour., 1856, ii, part i, p. 481. [36] Lyon méd., 1896, lxxxii, p. 289.

7. *Paracentesis of the Thorax and of the Abdomen.* In rare instances tapping of the chest, and more rarely still of the abdomen, is followed by the signs of acute pulmonary œdema, with the expectoration of large amounts of frothy albuminous material (albuminous expectoration). Originally it was believed that the albuminous expectoration was due to a wound of the lung, with a sucking up and the expectoration of the pleural fluid. This is not the case. The œdema results from an afflux of blood to the expanding lung, and a leakage of serum through the walls of the vessels, which by reason of long compression have become changed and rendered more permeable. In a paper upon this subject,[37] in which a bibliography will be found, I speak of this afflux as "congestion by recoil."

8. *Angioneurotic Œdema.* A case of sudden pulmonary œdema with coincident fugitive swelling of the face is reported by Hermann Müller,[38] who looks upon the pulmonary œdema as of the same origin, namely, angioneurotic, as of that of the face.

9. *Obscure Conditions of Questionable Causal Relationship.* Lavallée[39] reports a case of tabes dorsalis with two attacks of localized pulmonary œdema. There was arteriosclerosis, but no albuminuria and no valvular disease. In a case reported by Léopold-Lévy,[40] there was no other morbid condition than hysteria. Poppert[41] observed acute œdema of the lungs after ether anesthesia and collected seven similar cases from the literature.

PATHOGENESIS. Pulmonary œdema, whether acute or chronic, is brought about by leakage of serum through the capillary walls into the air vesicles and intervesicular tissues. In order that such leakage may take place, the pressure within the capillaries must be raised, or the permeability of the walls must be increased, or both factors must co-exist.

Many are the theories that have been advanced to explain the acute form of œdema. For purposes of clearness they may be classified as follows: (1) The periaortitic theory; (2) the cardiac theory; (3) the toxic vasomotor theory; (4) the infectious theory; and (5) the increased permeability theory.

1. *The Periaortitic Theory.* Huchard believes that the principal cause of acute pulmonary œdema is aortitis or periaortitis with extension of the inflammatory process to the cardiopulmonary plexus. The pathogenetic sequence, to quote his words, is as follows: "Disturbances of the innervation of the cardiopulmonary plexus by periaortitis; considerable augmentation of the vascular tension in the small circulation; acute or rapid insufficiency of the right ventricle." This is a satisfactory theory for those cases in which angina pectoris, Hodgson's disease, or other affections of the

[37] AMER. JOUR. MED. SCI., April, 1902.
[38] Corresp. f. Schweizer Aerste, 1891, p. 432.
[39] Journ. des Praticiens, May 14, 1897.
[40] Arch. de méd., 1895, clxxvi, p. 473.
[41] Deut. med. Woch., 1894, p. 719.

aorta exist; but it does not give an adequate explanation of those cases in which evidence of aortitis and general arterial disease is absent.

2. *The Cardiac Theory.* The cardiac origin of pulmonary œdema has its ablest defender in Welch, whose classical essay from the laboratory of Cohnheim has been misunderstood by more than one later investigator. As restated by Welch[42] in a recent communication, the theory is as follows: "Pulmonary œdema is due to a disproportion between the working power of the left ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart. Such disproportion may be brought about by paralysis or by spasm of the left ventricle." The salient feature of this theory then is a difference in the amount of blood thrown out by the two ventricles; the left expelling a little less in a given time than the right. As a result some blood remains behind in the left auricle; this reacts upon the pulmonary veins, so that they cannot empty themselves completely; consequently, there is a rise of pressure in the pulmonary circulation to a degree sufficient to bring about a transudation of fluid through the capillary walls.

The attacks upon this theory by Grossmann, who has produced pulmonary œdema with muscarin, by Sahli, and by Löwit are answered by Welch in the communication referred to, and need not be taken up here. Meltzer[43] has ingeniously applied Welch's theory to an explanation of the pulmonary œdema following adrenalin injection. He holds that in consequence of the great obstacle caused by the considerable constriction of all the smaller blood-vessels of the body, the left ventricle is incapable of throwing out all the blood that it receives from the pulmonary veins, while, on the other hand, the right ventricle, stimulated by adrenalin, unloads with increased energy upon the lungs all the blood which the contracting vessels drive into it.

3. *The Toxic Vasomotor Theory.* According to this theory, which is advanced by Bouveret,[44] acute pulmonary œdema is due to the action of toxic substances on the pulmonary vasomotor mechanism. There is doubt among physiologists whether the pulmonary arteries possess a vasomotor nerve supply, although Francois-Franck[45] seems to have shown that such an one does exist, and Hofmann[46] considers it practically demonstrated that the pulmonary vessels have vasomotor nerves, though their influence is not great.

The toxic theory is useful in explaining the acute pulmonary œdema of some cases of Bright's disease, that of angioneurotic

[42] Meltzer, Amer. Med., 1904, viii, p. 19, 59, 151, 191.

[43] Loc. cit. [44] Loc. cit.

[45] Arch. de Physiol., 1895, p. 816, quoted by Hofmann in Handbuch der Physiol. des Menschen, Nagel, p. 298.

[46] Handbuch der Physiol. des Menschen, Nagel, p. 300.

œdema, and, perhaps, that of pregnancy when there is no valvular or vascular disease.

4. *The Infectious Theory.* Caussade, Milhit, and Israel de Jong[47] have recently described a subacute œdema accompanying diverse pulmonary affections and possessing a more or less epidemic character. The expectoration is albuminous, frothy, not sanguinolent, and is easily differentiated from that peculiar to the disease, *e. g.*, bronchitis or pneumonia, with which the œdema happens to be associated. In the sputum the pneumococcus, usually of a virulent type, is present; whence the authors conclude that it is the cause of the œdema. Chloride retention and the neuroarthritic diathesis are predisposing factors.

The mere presence of the pneumococcus hardly possesses the importance the authors give to it, for such presence is to be expected when the œdema is an accompaniment of inflammations of the lungs that are known to be associated with this organism. The possibility of an infectious pulmonary œdema is, however, undeniable. It is probably present at some stage of all acute inflammations of the lung; but the type of œdema under consideration here does not bear the stamp of an infectious origin. The sudden onset of the attacks—their brevity, their subfebrile or afebrile character—militate against such a view.

5. *The Increased Permeability Theory.* Increased permeability as the sole cause of acute pulmonary œdema, as advocated, among others, by Martin,[48] is not adequate; but in conjunction with increased blood pressure it becomes an important factor, especially in the form of pulmonary œdema following paracentesis of the thorax.

PATHOLOGY. Renaut[49]—who is of opinion that both anatomically and clinically acute pulmonary œdema possesses an individuality that indicates a special pathogenesis—finds that the principal lesion is a serous inundation of the pulmonary alveoli. The alveolar fluid may be slightly fibrinous. White cells are abundant, sometimes to such an extent as to resemble a pneumonic exudate. That the entrance of the liquid into the alveoli has occurred violently under pressure is shown by the many points of rupture in the alveolar walls. The epithelium disappears within the limits of the œdema, having been forced off by the sudden eruption of fluid. The capillaries of the alveolar walls are flattened and rendered impermeable by compression, and, hence, are devoid of red cells. The large pulmonary and bronchial veins are, however, engorged with blood. The lymphatic spaces under the pleura are also distended.

Coplin,[50] whose study is the most recent, finds a finely granular

[47] Bull. et mém. de la Soc. méd. des Hôp. de Paris, February, 1906, p. 160.
[48] See Hewlett, Intercolonial Medical Journal, 1903, p. 611.
[49] Loc. cit.
[50] Loc. cit

deposit in the distended air vesicles and interstitial tissue, representing an albuminous fluid coagulated by the fixative. The capillaries usually show no conspicuous overdistention, and are frequently empty. The septal walls are often loosened and their tissues dissociated and infiltrated with mononuclear cells. The cell content of the air vesicles and interstitial tissue is subject to considerable variation; in some cases the erythrocytes are plentiful, and in others, not; polymorphonuclear leukocytes are at times abundant, and then bacteria are also present. In other cases again the cells are of the mononuclear type. Unlike Renaut, Coplin holds that detached vesicular epithelium can always be demonstrated. In some cases there is a marked swelling of the submucosa of the smaller bronchi and bronchioles, with a consequent narrowing of the lumen. The elastica is often stretched and the subserous and interstitial lymph vessels are distended.

SYMPTOMATOLOGY. One of the most striking features of acute pulmonary œdema is the suddenness of its onset, often in what appears to be a state of good health. The patient is seized, usually at night, with a sensation of oppression and suffocation accompanied by a fear of dissolution. The breathing is labored and of a rattling character; the dyspnœa, or orthopnea, intense; the countenance either livid or pale and bedewed with sweat; cough may be harassing, or it may be entirely absent. In typical cases there is a copious, frothy, albuminous expectoration which may be expelled in gushes from the mouth and nose, and may reach the amount of one or two liters during an attack. Often it is blood-tinged, and in one of my cases (II) it had the appearance of raspberry vinegar; sometimes it is whitish like bronchial secretion. The action of the heart and the pulse are feeble in some cases, as in the two with asthma here reported; the pulse, however, may be full and bounding. Over the lungs the characteristic subcrepitant and bubbling rales of œdema are heard; not rarely, they are most abundant over the upper parts, while in the ordinary œdema they are most numerous over the lower lobes posteriorly.

The first attack of œdema may be fatal, like the first attack of angina pectoris. More frequently the first attack is not fatal, and is followed by numerous others, all presenting a striking uniformity and each placing the patient in imminent danger of death. For some reason the paroxysms are generally nocturnal, and not rarely they set in during sleep. The average duration varies from three to six hours; some cases last twelve to twenty-four hours; in the extremely fulminant types, as in Case I of my series, death may take place within ten or fifteen minutes, the patient literally drowning in his own juices.

Brouardel[51] has pointed out the medicolegal importance of these

[51] Loc. cit.

hyperacute cases in which sometimes there is no expectoration, death taking place by suffocation before the patient has a chance to rid himself of any fluid. As to the number of attacks, the case of Lissaman[52] with seventy-two seems to hold the record. It is important to bear in mind this tendency to recurrence, so as to give a reasonable prognosis, and to be prepared to treat the attacks on a definite, well-considered plan.

Cerebral symptoms may be present, as in Case II, in which aphasia and hemiplegia complicated the attack and outlasted it for some time. Delirium, convulsions, and coma have also been noted.

DIAGNOSIS. Acute pulmonary œdema must be distinguished from (*a*) asthma; (*b*) pulmonary embolism; (*c*) acute dilatation of the heart; and (*d*) uremic asthma.

Asthma. From asthma, acute pulmonary œdema may be distinguished by the fact that in the former there is very little expectoration during the attack, and is established only when the seizure has passed off, and is limited to a small amount of glairy material or a few mucous pellets. The piping rales of asthma are different from the mucous, bubbling rales of œdema.

Pulmonary Embolism. In pulmonary embolism there is an embolic source; expectoration is developed later than in acute pulmonary œdema, in which it usually coincides with the onset of dyspnœa; when once established in embolism it is less abundant and more definitely bloody than in pulmonary œdema.

Acute Dilatation of the Heart. The dyspnœa and cyanosis in acute cardiac dilatation are rarely as intense as in acute pulmonary œdema. There may be œdema of the lungs; the difference here is perhaps only one of degree. In typical cases of acute pulmonary œdema the dominant feature is the inundation of the lung with fluid, and the dyspnœa is more directly mechanical than in dilatation of the heart.

Uremic Asthma. The dyspnœa in uremic asthma is seldom as severe as in acute pulmonary œdema, nor is it accompanied by profuse frothy expectoration, and, hence, not by the characteristic physical signs of œdema of the lungs.

TREATMENT. Treatment must be prompt to be effective. The best results are obtained by venesection. Merklen,[53] with great enthusiasm, says, "c'est l'unique salut." The abstraction of a small amount of blood usually suffices, though in rare instances as much as from 400 to 600 c.c. has to be taken. When bleeding cannot be done, or in addition thereto, dry cups may be used. Half a dozen wineglasses, in which air has been rarefied by burning alcohol, should be placed over the back; and if the patient is turned on his side several can be put on the front of the chest at the same

[52] Loc. cit. [53] Loc. cit.

time. If there is much nervous excitement, and a terrifying feeling of impending death, a small dose of morphine should be administered hypodermically. Authors, it must be admitted, differ as to the value of morphine. Hewlett recommends it; Steven condemns it. Lissaman found chloroform eminently successful in his remarkable case. When the pulse is feeble and asystole is threatened, diffusible stimulants, such as whiskey, ammonia, and hypodermic injections of camphor, are useful. Crummer ascribes the favorable outcome in his case to adrenalin chloride; but as far as this drug is concerned, the experimental observations of Bouchard and Claude,[54] of Meltzer, and of Coplin, who found that it could produce œdema in the lower animals, ought to make us cautious. Nitroglycerin suggests itself as a remedy in those cases in which there is every evidence of arterial hypertension, namely, in the arteriosclerotic and renal types. Oxygen is an agent of value when there is much cyanosis.

As I have said before, the likelihood of recurrence should be borne in mind, and should be made clear to the relatives of the patient. Where possible an intelligent member should be instructed in the method of applying dry cups, and, perhaps, in the use of the hypodermic syringe. Such precautions commend themselves more especially because the attacks generally occur at night, when it may be difficult to obtain medical aid at once.

Report of Cases: Case I.—Mrs. L., aged forty-six years; numerous attacks of acute œdema coming on without apparent cause. First attack in 1902, two days after death of mother; lasted one and one-half hours. No albuminuria in the beginning, later small amount of albumin, urine pale, low specific gravity, casts from time to time. Attacks characterized by dyspnœa, rattling breathing, mucous rales, sense of fear and terror, high tension pulse. Patient neurotic and subject to laughing and crying spells. Death occurred, December, 1905, in an attack lasting ten minutes, during which frothy, bloody fluid gushed from mouth and nose. Autopsy: Chronic interstitial nephritis, hypertrophy of the heart; intense pulmonary œdema, fresh petechial hemorrhages in the pleura and pericardium.

Case II.—Mr. W., aged seventy-two years; always healthy. Seized suddenly one night with intense œdema of the lungs; chest filled with moist rales; reddish, frothy fluid gushing from mouth; dyspnœa, collapse, unconsciousness, paralysis of right arm and leg, pulse irregular, reduplication of first sound at apex. Marked arteriosclerosis, urine (catheter) albuminous. Disappearance of pulmonary signs in two or three days, palsy lasting a little longer; eventual recovery. Another attack a month later, January 23, 1904, not so severe; recovery. Numerous others, usually with stupor or coma and variable degrees of fleeting palsy and aphasia. Last

[54] Comp. rend. de l'Acad. des Sciences, December, 1902, p. 928.

attack, March 19, 1904, at 3 A.M.; intense dyspnœa, unconsciousness, fluid gushing from mouth and nose, paralysis of right arm; partial restoration of consciousness following venesection. Death, no autopsy.

CASE III.—Mrs. McC., aged forty years; asthma of several years' standing. During the past winter and spring repeated attacks of intense dyspnœa with rattling breathing, frothy expectoration, bubbling rales, alarming collapse, with pallor, feeble pulse, clammy skin. Attacks entirely different from asthmatic paroxysms, but occurring during asthmatic periods. A number of attacks within two or three months. None since going south.

CASE IV.—Miss I. C., aged twenty-five years; asthmatic. Without apparent cause seized at midnight with intense dyspnœa and fear of impending death; lips cyanotic, face ashen pale, skin clammy, no pulse at wrist, respiration rattling, chest filled with bubbling rales, frothy fluid slightly tinged with blood gushing from mouth and nose. Urine normal. Attack subsided by morning; extreme prostration for several days; one slight recurrence while still in bed.

CASE V.—Mrs. N. S., widow, aged fifty-eight years. For three or four years attacks of anginoid pain in precordium with radiation into left arm. Attacks always associated with orthopnœa and signs of pulmonary œdema; the latter at times confined to left lung, generally bilateral. Best results during attacks from dry cupping and nitroglycerin. Death from cardiac dropsy, no autopsy.

CASE VI.—Mrs. S., aged thirty-eight years; pregnant seven months —eighth pregnancy. Seized without warning and without previous exposure with an attack of intense dyspnœa and a feeling of oppression and anxiety. There was a great deal of wheezing and cyanosis, harassing cough, and alarming prostration. My first impression was that the patient had asthma; but antiasthmatic treatment had no result. The rales, which had been dry, soon became moist and bubbling, and a free, whitish, frothy expectoration developed. The patient had never had asthma nor any other illness; had passed through five labors and three miscarriages without a doctor, a midwife only attending. There was no history of previous kidney disease; nevertheless, the urine was loaded with albumin, but free from casts. The heart presented nothing abnormal; there was no arteriosclerosis. Her condition becoming worse, and as she seemed in danger of suffocation, Dr. E. E. Montgomery was called in consultation, and it was agreed between us that labor should be promptly induced. Under ethyl-chloride anesthesia an attempt was made to stretch the mouth of the womb, but it could not be done sufficiently, and it was thought best to introduce a piece of gauze and await developments. Free bleeding occurred during the stretching. To our surprise labor did not follow, but the patient rapidly improved, and within twenty-four hours had practically recovered from her dangerous condition. The urine cleared up entirely within a few

days. Six weeks later, without any warning, the œdema returned. I promptly bled her from the elbow, with the most happy result. Her confinement is expected at any day.[55]

CONCLUSIONS. 1. There is an acute pulmonary œdema that comes on without any apparent exciting cause and often kills in a short time.

2. Recovery from an attack is frequent; but there is a striking tendency to recurrence, subsequent attacks being similar to the first. They set in suddenly, usually at night, and place the patient's life in jeopardy.

3. The clinical causes are various: arteriosclerosis and cardiac and renal disease are most important.

4. The pathogenesis is obscure; vasomotor disturbances and a disproportionate activity of the two ventricles (the right predominating) are the chief factors.

5. The chief symptoms are agonizing dyspnœa, cyanosis, cough, expectoration of frothy albuminous fluid, and profound prostration. Over the lungs, often more over the upper than the lower portions, the characteristic moist rales of edema are heard.

6. The most valuable remedies are bleeding, dry cupping, and cardiac stimulants.

7. The condition is of sufficient importance to warrant its having a special chapter in the text-books of medicine.

THE NATURE OF APLASTIC ANEMIA AND ITS RELATION TO OTHER ANEMIAS.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

APLASTIC anemia was first described by Ehrlich[2] in 1888. Since that time isolated cases have been reported and recently the condition has received considerable attention. The following typical case occurred in the University Hospital in the service of Dr. Stengel, to whom I am indebted for the clinical data.

J. C., female, aged thirty-three years, white, married, was admitted

[55] Since writing this she was delivered without any difficulty by Dr. V. A. Loeb, to whom I transferred her for this purpose; she has had no other attacks.

[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

[2] Charité Annalen, 1888, xiii.

to the University Hospital December 18, 1905, complaining chiefly of palpitation of the heart and vomiting after taking food.

Previous Medical History. The patient had measles, whooping-cough, and chicken-pox during childhood; diphtheria at twenty-two years; "congestion of the lungs" at twenty-five years. Menstruation began at eleven years, and has always been regular and at times painful. For the past eleven years, since her last child was born, the discharge has lasted about a week and has been profuse. The patient says that until the onset of the present illness she has always been robust.

Social History. The patient was married at the age of nineteen years, and is the mother of two healthy children, respectively twelve and eleven years of age. She had one miscarriage three years ago, apparently induced by severe exertion. Her work has been confined to household duties.

Family History. The patient's father died of "liver abscess" at the age of thirty-eight years. Her mother is living and well at fifty-seven years. Four sisters are living and well. There is in the family no history of tuberculosis, cardiac or renal disease, or neoplasm, and no condition similar to that of the patient.

History of Present Illness. The present trouble dates from about eight weeks ago, when the patient noticed that she was becoming pale, objects appeared yellow to her, and she was constantly fatigued. Six weeks ago she began vomiting after taking food. This vomiting was inhibited by her lying down. Shortly after the vomiting commenced cardiac palpitation and dyspnœa on the slightest exertion made their appearance, and the patient noticed that she was becoming progressively paler and weaker. She judges that in the past eight weeks she has lost about twenty pounds. During the last week she has had six attacks of temporary unconsciousness lasting about five minutes each. They were induced by no apparent cause. She has not fallen in the attacks, has not bitten her tongue, and has had no convulsive movements during the attack. Her appetite is poor and the bowels constipated. She has sour eructations and vomits on the slightest exertion or excitement. She has noted no discharge of blood from the mucous membranes. The feet have not been swollen.

Physical Examination. The patient is a large-framed woman with subcutaneous fat well preserved. The contrast between the degree of nutrition and the degree of anemia is very striking. The skin is of a lemon-yellow color, the mucous membranes are universally pale.

There are no areas of hemorrhage in the skin or visible mucous membranes. There is no enlargement of the thyroid, or of the cervical, axillary, or epitrochlear glands. No jaundice. Pupils are equal and react sluggishly to light. The patient complains of some loss of vision in the left eye. Teeth are imperfect and carious. Thorax is well-formed. Pulmonary resonance extends anteriorly

from one inch above the clavicle to the lower border of the sixth rib in the midclavicular line on the right; to the middle of the fourth rib on the left; posteriorly on the right, to the tenth dorsal vertebra; on the left, to the angle of the scapula. Below the angle of the scapula the resonance is somewhat impaired down to the tenth dorsal vertebra. In this area fremitus is diminished and breath sounds are feeble. No rales are heard. This area of diminished breath sounds extends anteriorly to the midaxillary line. In the remaining pulmonary area the breath sounds and fremitus are normal. The usual band of resonance over the shoulder is present on both sides. The physiological difference in breath sounds between right and left apex is less marked than usual.

The right border of the heart dulness is at the right border of the sternum; upper border, middle of fourth rib; left border, one inch outside of the left midclavicular line in the fifth interspace. The apex-beat is in the fifth interspace three-fourths of an inch inside of the midclavicular line. No thrills are present. There is a soft systolic murmur at the apex, heard also at the base, and most intense at the fourth interspace one inch to the right of the sternum. There is a slight accentuation of the pulmonic second sound. There is a continuous murmur heard over the innominate artery resembling a venous hum in its rhythm. There is also a dull venous hum high in the neck, over the jugular vein.

The abdominal walls are thick, but the abdomen is neither distended nor retracted. The liver dulness extends from the lower border of the sixth rib to within one inch of the costal margin in the midclavicular line. It is not palpable. Neither kidney is palpable. No tumor is discovered in the abdomen. The spleen is not enlarged, extends from the eighth to the tenth rib. It is not palpable. Nervous examination reveals no irregularities of reaction or sensation.

Urine Analysis. Amber, clear, slightly acid; specific gravity, 1010; slight trace of albumin; no sugar.

Gastric Analysis. Free HCl, 36. Total acidity, 64. No lactic acid. No Oppler-Boas bacilli.

Feces Analysis. Stool is yellow, hard, and alkaline. Contains considerable vegetable detritus, a small amount of casein, triple phosphates, and a small amount of soap. Bile is present. There is no occult blood and no indication of the presence of parasites.

Blood Examination. Hemoglobin, 10 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 2560; color index, 0.62. Differential count: lymphocytes, 67 per cent.; polymorphonuclear neutrophiles, 27 per cent.; polymorphonuclear eosinophiles, 0.4 per cent.; large mononuclear leukocytes, 3.5 per cent. No myelocytes were found. In counting over 1000 leukocytes, one normoblast was found. Despite repeated searches no megaloblasts were

found. There were no microcytes. Very slight poikolocytosis, and no anisocytosis were found. Subsequent examination of the blood revealed but trivial variations from this count.

Ophthalmoscopic examination revealed a well-marked, low-grade neuroretinitis, with numerous hemorrhages of various size and shape lying in the nerve-fiber layer, and a few more deeply placed hemorrhages. The swelling of the left nerve head and obscuration of its edges was more marked than in the right eye.

Without the appearance of any new noteworthy symptoms, the patient grew progressively weaker and died with symptoms of œdema of the lungs eight days after admission, or approximately nine weeks after the onset. Permission for the autopsy, performed four days after death, was obtained through the efforts of Dr. F. H. MacFarland, to whom I am deeply indebted.

Autopsy. The macroscopic findings briefly stated were as follows: The body of a well-formed, well-nourished, adult female. Height approximately five feet three inches. Weight about one-hundred and thirty-five pounds. Subcutaneous fat moderately abundant, light yellow in color. Muscles of fair consistency and pale. The left pleural cavity contained 400 c.c. of serosanguineous fluid; the right pleural cavity approximately 200 c.c. of fluid of the same character. There was œdema of the lungs and fatty degeneration of the heart muscle. There were no valvular defects. In the pelvic peritoneal cavity were 200 to 300 c.c. of dark-red, fluid blood containing one small clot. The liver was anemic and fatty; the spleen pale, firm, and not enlarged; the kidneys pale and fatty. Aside from pallor of the mucous membranes the gastrointestinal tract presented no abnormalities. There were no evidences of the presence of parasites. In the mesentery and retroperitoneal tissues a few hemolymph nodes were found, light reddish-brown in color, and of the size of small beans. The marrow of the ribs was light yellow in color; that of both the diaphysis and epiphysis of the tibia, fatty and extremely pale.

Histological Examination. There was fatty degeneration of the heart muscle in the form of extremely fine globules of fat, and a considerable hemosiderin deposit, mostly in the protoplasm of the cells at both poles of the nucleus. The section of liver showed a marked fatty change in the form of large globules confined almost exclusively to the central half of the individual lobules. There was an extensive deposit of hemosiderin occurring diffusely throughout the liver cells. In the section of spleen, there was noted a moderate proliferation of endothelium within the pulp. The follicles were prominent but apparently not hypertrophied. A few normoblasts were visible in the section. In the kidney the epithelium of the tubules of the cortex showed some disintegration and in many areas was detached from the basement membrane. Numerous small fat globules were present in the epithelium of the tubules,

especially toward the free margins of the cells. The lumina were filled with a granular exudate including, here and there, shadows of red blood corpuscles. The hemolymph glands showed the peripheral sinuses to be small and there was some endothelial proliferation in the pulp. Smears and sections were made of the bone-marrow of the shaft of the tibia near the epiphysis. They both showed a large amount of fat, a very few normoblasts and normocytes, an absence of megaloblasts, a moderate number of lymphocytes, and a few myelocytes. No polymorphonuclear leukocytes could be identified.

I have succeeded in collecting from the literature ten cases in which the clinical phenomena and postmortem findings warrant their being considered cases of aplastic anemia. They are as follows:

CASE I.—Bloch.[3] Female, aged sixty-three years; first symptoms noted, weakness and pallor; duration, six weeks. Blood: hemoglobin, 28 per cent.; red blood corpuscles, 1,970,000; leukocytes, 3250. Differential count: lymphocytes greatly preponderating; no nucleated red blood corpuscles; a few microcytes; no megalocytes; color index, 0.71. Postmortem findings: marrow of long bones showed no lymphoid hyperplasia; in marrow of ribs there were no megaloblasts. Prominent clinical feature: four days before death hemorrhage from buccal mucous membrane.

CASE II.—Bloch.[4] Female, aged fifty-three years; first symptom noted was weakness. Blood: severe anemia, marked reduction in leukocytes, those persisting being almost entirely lymphocytes. No megaloblasts; after prolonged search a few normoblasts were found. Postmortem findings: marrow of shafts of long bones pale and fatty. Marrow of epiphyses of normal red color. Prominent clinical feature: numerous gastric hemorrhages occurred during the course of the disease.

CASE III.—Ehrlich.[5] Female, aged twenty-one years; metrorrhagia eighteen days before onset. Blood: hemoglobin, very low; red blood corpuscles, 213,360; white blood corpuscles, greatly reduced. Differential count: lymphocytes, 80 per cent.; polymorphonuclear neutrophiles, 14 per cent.; large mononuclear leukocytes, 3 per cent.; eosinophiles, 0; no nucleated red blood corpuscles. Postmortem findings: bone-marrow yellow in shafts of long bones, slightly pinkish in diaphyses. No megaloblasts. No normocytes. Very few normoblasts and myelocytes. No polynucleated granulated cells.

CASE IV.—Engel.[6] Female, aged thirty-one years; shortly before onset blood noted in stools and hemorrhage from gums; duration, three weeks. Blood: hemoglobin, 18 per cent.; red blood corpus-

[3] Ziegler's Beiträge, 1903, xxiv, 331.
[4] Ibid.
[5] Loc. cit.
[6] Ztschr. f. klin. Med., 1900, ii.

cles, 2,115,000; white blood corpuscles, greatly reduced. Differential count: small lymphocytes, 90 per cent.; polymorphonuclear neutrophiles, 7 per cent.; no microcytes; no macrocytes; no nucleated red blood corpuscles. Color index, 0.42. Postmortem findings: diaphyses and epiphyses of long bones yellow and fatty. Microscopically, nothing but fat. Marrow of ribs gray and watery. No cells present. Prominent clinical feature: there was a doubtful history of swallowing of corrosive shortly before the onset of symptoms. Chief complaint was weakness.

CASE V.—Evans and Halton.[7] Male, aged thirty-six years; first symptoms noted shortly after bleeding from nose lasting two and one-half hours; duration, two months. Blood: hemoglobin, 10 per cent.; red blood corpuscles, 770,000; white blood corpuscles, 2300. Differential count: polymorphonuclear neutrophiles, 6 per cent.; small lymphocytes, 90 per cent.; large lymphocytes, 4 per cent.; eosinophiles, none; no nucleated red blood corpuscles. No marked poikilocytosis. Shortly before death two nucleated red blood corpuscles were found; color index, 0.65; actual number of lymphocytes, 2070. Postmortem findings: skull bones showed fatty marrow with very few cells. Prominent clinical features: chief complaint was weakness and faintness.

CASE VI.—Hirschfeld.[8] Female, aged twenty-eight years; onset shortly after delivery; duration, nine months. Blood: red blood corpuscles, 1,200,000; white blood corpuscles, 3600. Differential count: small lymphocytes, 72 per cent.; no eosinophiles; no nucleated red blood corpuscles; actual number of lymphocytes, 2592. Postmortem findings: bone-marrow universally yellow; bone-marrow was composed chiefly of small lymphocytes, a very few granulated cells, and a few normoblasts. Prominent clinical features: numerous small hemorrhages into the skin, mucous membranes, and retina occurred during the course; menstruation was extremely profuse.

CASE VII.—Muir.[9] Male, aged fourteen years; the first symptoms noted were vomiting of blood, bleeding from nose, and hemorrhages into skin; duration, eleven weeks. Blood: hemoglobin, 12 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 7000. Differential count: lymphocytes, 70 per cent.; polymorphonuclear neutrophiles, 25 per cent.; no nucleated red blood corpuscles; color index, 0.75; actual number of lymphocytes, 4900. Postmortem findings: bone-marrow fatty; very few nucleated red blood corpuscles or other normal cells of bone-marrow.

CASE VIII.—Pasteur.[10] Male, aged twenty-four years; first symptom was pain in epigastrium; duration, seven weeks. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,090,000; white blood corpuscles, 2600. Differential count: lymphocytes, 74 per

[7] Jour. Amer. Med. Assoc. 1905, i, 1195.
[8] Deut. med. Woch., 1904, xxii, 650.
[9] Brit. Med. Jour. September 29, 1900.
[10] Lancet, November 21, 1903.

cent.; polymorphonuclear neutrophiles, 20 per cent.; hyaline and transitional cells, 6 per cent.; no megaloblasts; color index, 0.91; actual number of lymphocytes, 1924. Postmortem findings: bone-marrow, pale; no polymorphonuclear leukocytes.

Case IX.—Zeri.[11] Female, aged fifty-seven years; first symptoms noted were hemorrhages into skin; duration, six months. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,300,000; white blood corpuscles, 3580. Differential count: polymorphonuclear leukocytes were scarce in comparison to lymphocytes; no macrocytes; no megaloblasts; two normoblasts were found; color index, 0.76. Postmortem findings: marrow of long bones yellow in both diaphysis and epiphysis; the same in costal and vertebral bones. Prominent clinical features: during the course of the disease patient had prolonged epistaxis and numerous hemorrhages into skin.

Case X.—Zeri.[12] Male, aged forty-six years; onset preceded by diarrhœa; duration, three months. Blood: hemoglobin, 38 per cent.; red blood corpuscles, 1,423,000; white blood corpuscles, 2700. Differential count: polymorphonuclear leukocytes and transitional cells, 57 per cent.; eosinophiles, 0; later moderate poikilocytosis; a few microcytes and macrocytes; no nucleated red blood corpuscles; color index, 1.33; actual number of lymphocytes, 1161. Postmortem findings: marrow of flat bones, orange yellow; of long bones, in both epiphysis and diaphysis, yellow and fatty; scarcity of polymorphonuclear leukocytes; normoblasts with multiform nuclei were present; in the marrow of the shafts of the long bones degeneration and proliferation of connective tissue.

Making a composite case from these ten cases and my own, we obtain one of the following characteristics: age, thirty-seven years; duration, three months. Blood: hemoglobin, 18 per cent.; erythrocytes, 1,116,600; leukocytes, 3574; lymphocytes, 73 per cent.; actual number of lymphocytes, 2393; color index, 0.77. It is readily seen that the more prominent features of such a case are sufficiently marked to furnish a very striking clinical picture, associated with unique postmortem findings.

The disease, as characterized by the cases quoted shows itself to be first manifested by symptoms common to any profound anemia: ready exhaustion, dyspnœa, disturbance of vision, tinnitus, nausea, and vomiting. In a strikingly large percentage of cases, considerable or numerous small hemorrhages occur shortly before, or coincident with, the onset of the symptoms of anemia, as noted by the patient. The patient usually remains fairly well nourished as far as the bulk of the fixed tissues, particularly the fat, is concerned, and there is a striking disharmony between the quality of the patient's blood and state of bodily nourishment. Usually without any prominent symptoms referable to any other system or function,

[11] Il Policlinico, s. m. fasc. vii, 1905. [12] Ibid.

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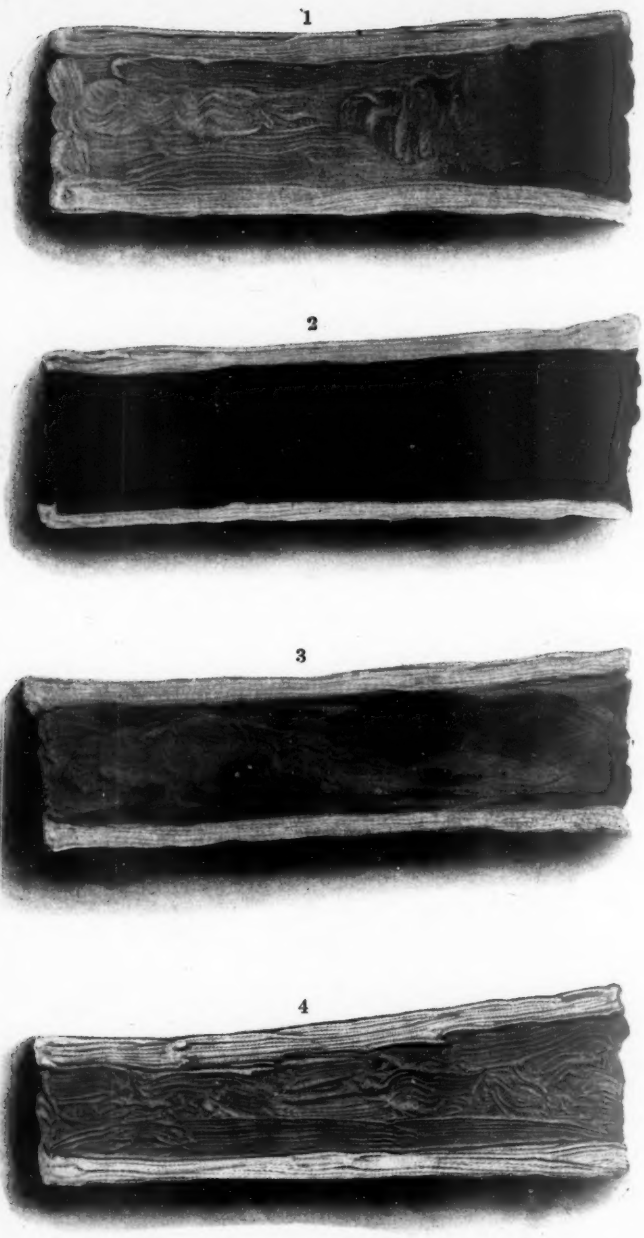

BONE MARROWS.—1. Normal. 2. Typical progressive pernicious anemia. 3. Scattered areas of megaloblastic degeneration in progressive pernicious anemia. 4. Aplastic anemia.

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the patient grows progressively weaker, and in from two to four months dies. Naturally the most noteworthy picture is afforded by the blood analysis, in which there is a profound reduction in the amount of hemoglobin and a somewhat less marked reduction in the number of red blood corpuscles, an absence or a remarkably small number of normoblasts, a total absence of megaloblasts, and a leukopenia associated with a relative lymphocytosis.

At autopsy, aside from the findings purely incidental to the grade of the anemia, there is the characteristic feature in the bone-marrow, which is intensely pale and fatty and lacks the evidences of blood regeneration.

A critical review of these more prominent symptoms immediately suggests the question that has been the source of some argument in regard to aplastic anemia, namely, its relation to progressive pernicious anemia. The onset of the disease, its course, excepting as to the rapidity of a lethal termination, the absence of any marked loss of substance in the fixed tissues, and the great reduction in the amount of hemoglobin and the number of red corpuscles, are common to both conditions. In our attempt to determine the relation between aplastic anemia and progressive pernicious anemia, let us discuss individually the phenomena at variance in the two conditions. Probably the most striking of these, and surely the most important, is the blood picture in which we find an almost complete absence in aplastic anemia of nucleated red blood corpuscles and the total absence of megaloblasts. Since the red corpuscles are a product of the bone-marrow, a consideration of them will necessarily involve a consideration of the bone-marrow. There is by no means a unity of opinion as to the primary effect of the etiological agent in pernicious anemia in its relation to the bone-marrow. Rindfleisch and Cohnheim[13] look upon the bone-marrow changes as primary, while others (Neumann, Litten, Orth) consider them as secondary, in the nature of an attempt on the part of the bone-marrow to compensate for the destruction of red blood corpuscles. Just as the character and number of the atypical red blood corpuscles vary in different cases of anemia, so does the character of the bone-marrow differ (see accompanying plate). In one case there is a red jelly-like marrow (megaloblastic degeneration) composed almost entirely of megaloblasts and associated with the presence of numerous megaloblasts in the circulating blood; in another case, but few megaloblasts and correspondingly little red marrow in the shafts of the long bones. In a case that I recently autopsied, there were a very moderate number of normoblasts and megaloblasts, and at the autopsy the shafts of the long bones were found to be fatty with islands of red scattered here and there through it. It is thus seen that deductions as to the condition of the bone-

[13] Virchow's Archiv, lxvii, 291.

marrow can frequently be drawn from a consideration of the cells of the circulating blood.

What of these relations in aplastic anemia? I have said that the blood shows an extremely limited number of nucleated red blood corpuscles, and we would consequently expect to find, as we in fact do, a pale bone-marrow in which the evidences of new blood formation are entirely wanting. We see, then, that in aplastic anemia there is a blood picture which is but a reflection of the condition of the bone-marrow, in which evidences of regeneration are entirely lacking, but in which there is no indication that the determining factor in the causation of the disease acts in any way different from that of the usual type of progressive pernicious anemia. It is but a difference in response of the organism to the causative agent.

What of the color index which in typical progressive pernicious anemia is considered to be characteristically high, and in aplastic anemia has been in all cases, excepting one, considerably below 1, and averages in all the cases 0.77? In progressive pernicious anemia, aside from megaloblasts, there are non-nucleated red blood corpuscles of considerably more than normal size, megalocytes. Laache has offered the usually accepted explanation for the high color index in progressive pernicious anemia in the large number of these abnormal cells present, which containing more hemoglobin than the normal cell naturally raise the color value. As has been remarked, in aplastic anemia there is usually little anisocytosis, and with the absence of both megaloblasts and megalocytes, it is readily seen why, on the basis of Laache's theory, the color index should not be raised above the normal. An interesting theory for the high color index in progressive pernicious anemia is proposed by Schaumann.[14] He considers that some of the iron deposited as hemosiderin in the liver and spleen is taken up by the existing corpuscles, used as a nucleus for the formation of more hemoglobin, and thus each individual corpuscle bears more than the normal amount. Some weight is lent to this view by experiments of Tallqvist.[15] In experimental anemias in dogs he showed that the color index was higher in cases of slow growing anemia than in those of rapid growth, and in the former the siderosis was greater than in the latter. This theory would also explain the low color index in cases of aplastic anemia, as they have almost all been of extremely rapid course.

Let us consider for a moment this more rapid course and invariably fatal termination of aplastic anemia with the course and termination in progressive pernicious anemia. We have seen that in aplasic anemia destructive forces are at work as in progressive pernicious anemia, but the regenerative process present in

[14] Berl. klin. Woch. 1899, Nos. 1 and 3.
[15] Ueber experimentelle Blutgiftanæmien, Berlin, 1900.

the latter is wanting in the former. If a destructive process be active and there be no constructive process to counteract it, it is but a natural consequence that, other things being equal, exhaustion will more readily result than if there be constructive changes.

Another feature at variance in the two conditions is the number of leukocytes and the proportions to one another of the various forms of leukocytes. In uncomplicated cases of progressive pernicious anemia the leukocytes average from 5000 to 6000; in aplastic anemia they average 3574. What is even more striking than this difference is the difference in the percentage of lymphocytes. In progressive pernicious anemia the lymphocytes vary from 37 per cent. (Strauss and Rohnstein[16]) to 31 per cent. (McCrae), while in aplastic anemia they average 73 per cent. A discussion of the principles underlying this variance must be prefaced by a few words concerning the origin of leukocytes. It is generally conceded that the granulated leukocytes, *i. e.*, the polymorphonuclear leukocytes and their progenitors, the myelocytes, have their origin in the bone-marrow; but there has been a vigorous discussion existing for some time as to whether the lymphocytes be the product of the bone-marrow or of the other more distinctly lymphatic structures, lymph glands, spleen, and lymphatic tissue of the gastrointestinal tract. Ehrlich believes firmly in the origin of the lymphocytes from true lymphatic structures, while others claim them to be of common origin with the granulated cells. That lymphocytes are formed in the bone-marrow there can be little doubt, for wherever lymphoid tissue is present, lymphocytes are produced; and, as was shown by Arnold and Ribbert, there is an element of lymphatic tissue in almost every organ of the body. So although lymphocytes may be produced in the bone-marrow by reason of the participation of the bone-marrow in the general distribution of lymphatic tissue, I do not believe that the production of lymphocytes is a specific function of it. Let us observe what bearing the lymphocytes in aplastic anemia have upon the question. We have seen that the red blood corpuscles and the granulated leukocytes, both admittedly products of the bone-marrow, are enormously reduced. But what of the lymphocytes? We have seen that in the average case of aplastic anemia there are 2393 lymphocytes, and it will be observed that this differs but slightly from the average normal number of lymphocytes, about 2200. Does it not seem irrational that if the lymphocytes be an integral part of the bone-marrow they should be so slightly affected and the other bone-marrow elements so profoundly reduced? As to the relation between the percentage of lymphocytes in progressive pernicious anemia as compared with that of aplastic anemia, I look upon it that in neither condition are they actually materially affected. In progressive pernicious anemia they are, on the average,

[16] Die Blutzusammensetzung bei den verschiedenen Anämien.

approximately 35 per cent. of the total number of leukocytes, 5000 to 6000, which is but little less than 73 per cent. of 3574, the total average number of leukocytes in aplastic anemia. The difference depends entirely upon the variations in the number of polymorphonuclear neutrophiles and in harmony with the generally more intense character of the lesions in aplastic anemia they are more markedly reduced than in the former.

In regard to the autopsy findings the essential differences in the two diseases lie in the bone-marrow, which, as we have attempted to show in the above analysis, manifests a complete failure of regeneration on its part.

Basing our deductions upon the above comparison, we thus see that progressive pernicious anemia is associated with regenerative processes which in aplastic anemia are lacking. As to the destructive processes, it has been shown by Hunter, Quincke, Pepper and Stengel that progressive pernicious anemia is primarily a hemolytic disease. That aplastic anemia is of the same nature, may be accepted by reason of the consistent occurrence of hemorrhages in practically all of the cases reported, and by reason of the hemosiderosis present in our case. It is unfortunate that in the previously reported cases no mention is made of this condition. We see, then, that the blood picture in aplastic anemia and the course of the disease are the result of two factors: the one the hemolysis, the other the failure of regenerative changes to compensate for this destruction. The failure of regeneration by the bone-marrow may be dependent upon one of the following three factors: first, a simple deficiency of the regenerative powers; second, an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; third, a true aplasia of the bone-marrow. If the latter be the case, the aplasia is probably of recent origin, for if it were of long duration there would, in all probability, have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

It will be necessary to discuss but briefly the relation that aplastic anemia bears to simple anemia. Lazarus looks upon aplastic anemia as a variety of simple anemia, basing his view upon the fact that aplastic anemia is most like simple anemia in the blood picture. A review of the cases that we have collected reveals the fact that in practically none of the cases has there been the history of the various organic diseases so frequently associated in an etiological way with simple anemia. It is true that hemorrhages do appear to have been more frequent and probably more profound in aplastic anemia than in progressive pernicious anemia, but that they stand in an etiological relation to aplastic anemia can scarcely be entertained. They have occurred throughout the course of the disease rather than precedent to it, and as Birch-Hirschfeld[17] has

[17] Verhandl. d. Congress f. innere Medizin, Wiesbaden, 1892, xi.

emphasized, the severity of the anemia stands in marked contrast to the amount of hemorrhage, though it must be admitted that in some cases when hemorrhages are small and numerous, and especially when they occur in the gastrointestinal tract, a calculation of the amount of blood lost is difficult or impossible; but the most important elements differentiating aplastic anemia from simple anemia are furnished by a consideration of the clinical features of aplastic anemia. It is an essentially pernicious disease in course, duration, and termination, and serves well to illustrate the futility of attempting the diagnosis of most blood diseases on the blood picture alone.

The exclusion from our list of a number of cases that have been reported as cases of aplastic anemia, or present otherwise features suggestive of this disease, requires some words of justification.

Senator[18] reports the case of a girl, aged thirteen years, complaining, chiefly of weakness and vertigo. The disease was of three months' duration, and the blood findings were as follows: hemoglobin, 8 to 10 per cent.; erythrocytes, 1,040,000; leukocytes, 8000; poikilocytosis; no nucleated red blood corpuscles; no eosinophiles. The majority of the white blood corpuscles were lymphocytes. Blood from the heart, taken at autopsy, showed 728,000 red blood corpuscles and 11,200 white blood corpuscles, of which 83.6 per cent. were lymphocytes. At autopsy the bone-marrow was found to be universally red, showing microscopically large numbers of lymphocytes and a few normoblasts. Two elements in this case tend to exclude it from the aplastic anemias. The one is the metaplastic bone-marrow, containing numerous lymphocytes, the other the occurrence clinically of a considerable actual increase of the lymphocytes, as is shown by the fact that 83.6 per cent. of 11,200 leukocytes were lymphocytes. Senator himself says of the case, after a consideration of the clinical and postmortem features, "we are thus dealing with a case of myelogenous pseudoleukemia, and according to the present-day terminology one of a pure medullary form, since the lymphatic glands were not at all, and the spleen to a very moderate degree, swollen."

Blumer[19] reports a case of twenty-two months' duration, occurring after the loss of considerable blood from hemorrhoids. The blood showed 20 per cent. of hemoglobin, 1,516,000 red blood corpuscles, and 4000 white blood corpuscles, of which 88.3 per cent. were lymphocytes. An average of one normoblast to a field was found. At autopsy the bone-marrow of the upper part of the tibia was yellow, that of the ends of the other long bones partly red and partly fatty. On the basis of a duration of twenty-two months, which is more than seven times the average duration, and the presence of a considerable number of normoblasts, in harmony

[18] Ztschr. f. klin. Med., lix, 1.

[19] Bull. Johns Hopkins Hospital, April, 1905.

with which is the partly red and partly yellow bone-marrow of the diaphyses, we feel justified in looking upon this as a doubtful case of aplastic anemia. It has more of the features, excepting for the percentage of lymphocytes, of a low grade normoblastic progressive pernicious anemia.

Schaumann's[20] case, which he reports as aplastic anemia, is very suggestive, but the data furnished in the report of the case are insufficient to warrant the diagnosis.

The case of Pane,[21] quoted by Zeri as a case of aplastic anemia, is doubtful. The meager clinical data furnished, associated with the finding postmortem of a splenic tumor, and hyperplasia of Peyer's patches and the solitary follicles of the intestinal tract, do not justify us in considering the case one of aplastic anemia.

Wolff's[22] case presents, as he himself says, "more features of an aplastic leukemia than an aplastic anemia."

Escherich[23] reports a case of anemia in a child, aged four years, that strongly suggests aplastic anemia. The disease was of six months' duration. The red blood corpuscles varied between 575,000 and 737,500; the hemoglobin between 10 and 15 per cent.; the leukocytes between 3500 and 7000. The statement is made that the majority of white blood corpuscles were lymphocytes. There was considerable poikilocytosis and macrocytosis and no nucleated red blood corpuscles. There was at first some swelling of the lymphatic glands in the region of the mastoid and in the left axilla. It is to be regretted that there was no postmortem examination to confirm the strong suggestion of its having been a case of aplastic anemia.

Kurpjeweit[24] has recently reported two cases of anemia in the aged, which present some features suggestive of aplastic anemia, especially the first case. However, the greatly enlarged spleen, measuring 18. 5 cm. x 12. 5 cm. x 6 cm., and the but moderately severe course of the disease, together with the lack of leukocytic examination in the case, will not permit of a diagnosis of aplastic anemia. The second case also had a remarkably large spleen, 800 grams. Lymphocytes did not preponderate, and the bone-marrow showed normoblastic regeneration.

Conclusions. 1. Aplastic anemia is a variety of progressive pernicious anemia.

2. The essential features of aplastic anemia are: a rapidly fatal course; a marked reduction in the number of red blood corpuscles; a greater proportionate reduction in the amount of hemoglobin, resulting in a low color index; a leukopenia with a relative lym-

[20] Volkmann's Sammlung klinischer Vorträge, n. f. No. 287.
[21] Riforma Medica, 1900, xvi, No. 4.
[22] Berl. med. Woch., 1905, xlii, No. 2.
[23] Wien klin. Woch., 1892, Nos. 13 and 14.
[24] Deut. Archiv. f. klin. Med., lxxxii, Nos. 5 and 6.

phocytosis; an absence of megaloblasts, and usually normoblasts. Postmortem: the characteristic finding is a pale bone-marrow in which the signs of erythrocytic and granulated leukocytic formation are wanting.

3. The differences between aplastic anemia and the usual form of progressive pernicious anemia result entirely from the absence of regenerative processes in the former.

4. The blood picture in aplastic anemia is the result of two factors, one the hemocytolysis, and the other the failure of regeneration on the part of the bone-marrow.

5. The failure of regeneration of the blood elements of the bone-marrow represents the result of one of the three following conditions: (*a*) A simple deficiency of the regenerative powers; (*b*) an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; and (*c*) a true aplasia of the bone-marrow. If there be a true aplasia it is probably of recent origin, for if it were of long duration there would in all probability have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

6. The relations of lymphocytes to leukocytes and red blood corpuscles in aplastic anemia lend evidence to the view that lymphocytes are not a specific product of the bone-marrow.

STUDIES IN THE NATURAL AND ARTIFICIAL INHIBITION OF PEPTIC DIGESTION.

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No matter how important the secretion of hydrochloric acid may be for the purpose of preparing the food for the action of pepsin, and for stimulating the production of pepsin and the secretion of the pancreatic, and probably of the intestinal juices, there can be no question, we think, that the actual work in the stomach of preparing the proteids for assimilation depends upon the peptic activity. Therefore it is exceedingly important in all cases of gastric disease to determine whether the peptic activity is normal or not, and whether, if it is normal under favorable experimental conditions, there may not be present in the gastric contents inhibitory factors which prevent, or make imperfect, the peptonization of the food.

A number of methods have been suggested for estimating the

peptic activity. Of these the only ones of value clinically are those of Hammerschlag and Mett. Both are good, and give results that are useful in diagnosis and for the purpose of controlling treatment. We have elsewhere stated our reasons for preferring the method of Mett. Our technique in the use of this method has already been described. It yields results that are practically the same as those of other investigators.

The object of the present investigation was to determine, first, the natural inhibitory factors in the gastric contents; second, the inhibitory action of certain substances, chiefly those used as food preservatives.

The natural factors may be substances secreted by the stomach itself, or products, either normal or abnormal, of the digestive activity. Danielewsky claims to have discovered a substance, antipepsin, which exists in the gastric mucosa. It inhibits the action of pepsin but does not destroy it; it may be extracted with weak acid solution; it is not destroyed by heating to 70° C. or even by brief exposure to 100° C. Hensel found that it is not precipitated by phosphotungstic acid. It is organic in nature, but not an albumin. A similar substance is obtained from various organs. Weinland and Schwartz have also studied this subject. The latter, by boiling a solution of pepsin, was able to demonstrate that it acquired inhibitory properties as a result of destruction of the pepsin and immunity of the antipepsin.

Nearly every type of food, the carbohydrates, the hydrocarbons, the proteids, and the products of their digestion, and the various mineral constituents, have been accused of inhibitory activity.

The method has undergone some trifling modifications in the course of the work. At first we used rather strong solutions of pepsin. In a quantity of 16 c.c., 5 c.c. consisted of 2 per cent. pepsin, and the remaining 11 c.c. of a dilution of the substance under examination, or, for the purpose of control, $\frac{n}{20}$ HCl. The pepsin was dissolved in $\frac{n}{20}$ HCl and the substance to be tested in the same solution, excepting in the case of liquid substances bulky enough to make it necessary to acidulate them to the same degree with concentrated HCl. The degree of inhibition that exists in strong pepsin solutions, however, is so great that we found the results were more uniform if weaker solutions were employed, and all our later experiments have been made with 1 c.c. of a 1 per cent. solution of pepsin and 15 c.c. of the test substance.

The preparation of the tubes, however simple, is of some importance. The best results are obtained with fairly thick-walled glass tubes of an internal diameter of between 1 and 2 mm. These are filled with albumin, boiled for five minutes, and, while boiling, rolled continually. The ends are then closed with sealing wax. The variations in the reading of these tubes are so slight as to be of no importance.

Our results, of course, exhibit only one phase of the subject, and that is the effect of the test substances upon peptic digestion under apparently favorable conditions for its manifestation. In the stomach a number of factors are at work altering the composition of the gastric contents. These are: The ingestion of food, water, or saliva; the secretion of gastric juice; the secretion of mucus; osmosis; the discharge of the stomach contents through the pylorus; and, occasionally, the regurgitation of the duodenal contents into the stomach. In the case of saline solutions osmosis becomes a very important factor, and probably if strong they are rapidly diluted.

The technical difficulties of studying the effect of various substances upon the peptic activity within the stomach are very great; nevertheless, we have attempted to overcome them in a series of experiments which is still fragmentary and incomplete. It must not be forgotten, moreover, that in all these experiments the peptic activity varies not in accordance with a simple numerical proportion, but in proportion to the square root of the degree of concentration of the pepsin. This law was first determined by Schuetz, working with an exceedingly cumbersome method, and afterward restated by Borissow. Samojloff found that it did not hold good for strong solutions, either in artificial pepsin solutions or the actual gastric juice. In the course of our work we have noted some very good illustrations of this law.

TABLE I.

Pure	2.2	(4.84)
1/2	2.4	(5.76)
1/4	2.2	4.84
1/8	1.4	(1.96)
1/16	1.1	1.21
1/32	0.8	0.64
1/64	0.5	0.25

TABLE II.

Pure	4.9	24.01
1/4	4	16
1/8	2.7	7.29
1/16	1.9	3.61

In both tables it will also be observed that in the pure gastric contents inhibition was present. We shall discuss this more fully in a subsequent paragraph.

Schuetz's law is exceedingly interesting. Why pepsin should show the peculiar quality of diminishing in activity according to the square root of the degree of dilution—a quality, so far as we know, possessed only by it and a few other ferments—has never been clearly elucidated. An hypothesis that has occurred to us would serve in a measure to explain it, although, aside from the fact of being a satisfactory explanation, there is no other proof of its correctness. This is, that the peptic ferment consists of discrete particles. Either these particles are in continual activity and mutually interfere with one another in their movements, or else they radiate activity and the emanations from different particles interfere. To our minds the former hypothesis seems by far the more satisfactory, but in either case increase in the distance between the

individual particles would cause an increase in their capacity for activity proportionate to the square of the distance, and inversely as the degree of concentration. Conversely, the effect of concentration would be to increase the peptic activity not directly, but in proportion to the square root of the degree of concentration. This accords with the results obtained by experiment. In high concentrations the inhibition is greater than the law would indicate, as is clearly shown in the following experiment:

Pepsin 1 per cent.	6.7	Pepsin 1/4 per cent.	4.3
	Pepsin 1/16 per cent.	2.5	

If, in the gastric contents, the inhibition were of moderate degree the diminution of peptic activity in concentrated solutions would be sufficient explanation for it. Investigation, however, has shown that the inhibition is actually much greater than can possibly be explained by any concentration of the solution, being sometimes absolute, when pure gastric contents is tested, although in lower dilutions peptic activity is fairly strong. The following table of a series of cases taken in the order of their testing illustrates this fact very clearly. It has been arranged as follows: In the first column, the case number; in the second, the total acidity of the gastric contents under investigation; in the third, the peptic activity of the pure gastric contents; in the fourth, the peptic activity of the gastric contents diluted 1 in 4; in the fifth, the peptic activity of the gastric contents diluted 1 in 16. It did not seem necessary to insert the results of intervening dilutions, although they were usually made.

Case No.	T. A.	Pure.	1/4	1/16
173	96	8.6	6.6	5.5
66	52	0.0	5.2	2.8
168	43	4.1	5.5	3.2
188	145	5.6	7.1	5.9
118	90	7.8	7.5	4.3
151	150	2.2	2.2	1.1
134	60	8.9	8.2	5.4
151	150	8.3	7.9	5.8
151	150	3.7	5.4	3.7
134	60	0.7	3.5	3.2
155	106	7.4	7.3	5.3
139	58	0.0	...	2.2
134	90	0.8	4.5	4.8
110	136	2.4	...	1.9
124	40	3.2	2.4	1.2
118	72	5.2	3.1	1.7
H. C.	90	2.2	2.5	1.6
H. C.	67	4.9	4.0	1.9
H. C.	38	0.5	...	1.0
60	44	2.6	1.8	1.1
73	110	2.4	...	1.9
211	92	3.6	4.4	2.3
216	71	4.4	4.1	2.8

H. C. = hospital cases.

It will be seen that, according to Schuetz's law, the length of the column of albumin digested in the Mett tube should be, in the fourth column, twice that in the fifth, and in the third column, twice that of the fourth, or four times that of the fifth. In 5 cases the number in the fourth column is approximately twice as great as in the fifth, indicating that, in a dilution of 1 to 4, the inhibitory factors had been overcome. In no instance is the third column either twice as great as the fourth, or four times as great as the fifth. The average in the different columns is, for the third, 3.9 mm.; for the fourth, 4.8 mm., and for the fifth, 3.16 mm. In 2 cases the inhibition was complete, although in both digestive activity was present in higher dilutions (cases of achylia gastrica in which peptic activity was not manifest in the dilutions have been omitted). This table shows that the statement so frequently made, that in hyperacidity the peptic activity is at least normal, is entirely fallacious. In 1 of the negative cases the total acidity was 52, and in the other 58. In 2 cases, in which only a trace of digestion occurred in the pure gastric juice, the total acidity was 60 and 38. Inhibition was very pronounced in 1 case with a total acidity of 150, and in another with a total acidity of 145, and there was apparently an actual deficit in the peptic activity in the case with a total acidity of 136. These cases resemble in many respects achylia gastrica. It is obvious that in such cases the administration of alkalies alone can be of no benefit in restoring gastric digestion, but that the object of treatment should be to remove or diminish the inhibitory factors, because the results of the higher dilutions indicate that latent peptic activity exists in the undiluted gastric contents.

The literature upon the subject of inhibition by food and the products of digestion is not considerable. Nierenstein and Schiff believe that the carbohydrates have an active inhibitory power. Pawlow calls attention to the fact that the administration of oil greatly diminishes the secretion of the gastric juice, but he did not study its effects upon the digestive powers of the juice after secretion.

Pick is the only investigator who appears to have done much work upon this subject. His method differed in details from our own. He used a 2 per cent. solution of Merck's pepsin scales in $\frac{n}{20}$ HCl. Of this solution 20 c.c. were placed in a Stender dish with the Mett tubes, and the substance to be tested added in bulk. The whole was then placed in an incubator for twenty-four hours. Certain minor objections can be made to this technique. Excepting in a few cases it fails to determine the limits of inhibition. The substances added may alter the chemical reaction of the solution, or may act to a certain extent mechanically. The great advantage of his method is that it enabled him to make a large number of experiments within a comparatively short period of time, and therefore to cover more ground than could possibly have been

done had he made more elaborate studies. He explains inhibition strictly according to the theory of ions. The electronegative ions inhibit peptic activity, and, therefore, those chemical compounds in which they predominate diminish proteolysis.

We used, wherever possible, solutions of known strength of the substances employed, and made a series of dilutions of these solutions, so that by comparing the final results with a series of controls, and repeating the experiments, it was possible to determine the points at which inhibition became manifest, and was absolute.

The effect of proteids was studied in various ways. 10 c.c. of a 5 per cent. solution of egg albumen were added to 5 c.c. of a 2 per cent. solution of pepsin, the object being to determine whether the digestion of egg albumen inhibited the digestion of the Mett tubes. There was no inhibition. A cylinder of egg albumen 1 cm. in diameter was then coagulated by prolonged boiling, and disks 4 mm. in thickness were cut from it and placed in the Stender dishes in place of the albumen solution, it being thought that perhaps there was not enough albumen in the other experiment. No inhibition, however, was observed. A similar experiment was then performed, but the Mett tubes were added only after the albumin had been digested for twelve hours, at the end of which period it was in fact entirely dissolved. Twelve hours later the average digestion was 3.3 mm. and of the control tubes 5.3 mm., indicating active inhibition as a result of the presence of the products of proteid digestion. In order to deal with a measurable solution we used Witte's peptone. The following series show its inhibitory power. In the first table 5 c.c. of a 1 per cent. pepsin solution was employed, and in the second table 5 c.c. of filtered gastric contents with a total acidity of 80.

Per cent.	Pepsin.	g. c.	Per cent.	Pepsin.	g. c.
10	0.0	0.0	5/8	2.7	0.9
5	0.0	0.0	5/16	3.0	0.8
2½	0.2	0.4	Control	2.9	0.7
1¼	2.4	0.7			

g. c. = gastric contents.

This shows that inhibition is absolute if the peptone or albumose present amounts to 5 per cent. by weight of the total, that it is still considerable for 2.5 per cent., but that it practically ceases about 1 per cent. Pick also found that Witte's peptone inhibited gastric digestion. To what extent this inhibitory activity is manifest in the stomach is difficult to determine. The methods for precipitating albumose carry down pepsin also, so that it is impossible to decide whether the removal of the peptone would restore peptic activity or not; and dialysis is too slow to be practicable. It seems difficult to understand how, in the two or three hours that the food remains in the stomach, enough albumose can be formed to produce

a strong degree of inhibition, and there is no evidence to show that the inhibition is greater after a proteid meal than after an ordinary test breakfast of bread and water.

Somewhat akin to proteids is gelatin. We used the white transparent gelatin strips commonly employed in bacteriology. 1 c.c. of a 1 per cent. pepsin solution was employed as the digestant.

Per cent.	Pepsin.	g. c.	Per cent.	Pepsin.	g. c.
10	0.0	0.0	1/4	2.6	1.5
5	0.5	trace	5/8	2.5	1.7
2 1/2	3.0	1.2	Control	2.5	1.9

Presumably at a point slightly below 10 per cent. inhibition is absolute. It practically disappears at 2.5 per cent.

In testing carbohydrates we used first a solution of cane sugar dissolved in $\frac{n}{20}$ HCl. The digestant was 5 c.c. of a 2 per cent. solution of pepsin, in one series, and 5 c.c. of filtered gastric contents with a total acidity of 110, in the other series. Only one set of results in each series is given. Other series were practically the same.

Per cent.	Pepsin.	g. c.	Per cent.	Pepsin.	g. c.
10	1.0	0.0	5/8	2.2	2.5
5	1.7	2.7	5/16	3.1	...
2 1/2	2.2	2.4	Control	2.8	3.0
1 1/4	1.9	3.1			

In the pepsin group the digestive activity of one and one-quarter seems inaccurate. In three other series there was no diminution at this point. Practically, therefore, there is marked inhibition at 10 per cent., slight at 5 per cent., and little or none at 2.5 per cent.

In testing Merck's dextrose we used 5 c.c. of a 1 per cent. pepsin solution and 5 c.c. of filtered gastric contents with a total acidity of 80.

Per cent.	Pepsin.	g. c.	Per cent.	Pepsin.	g. c.
10	2.4	1.1	5/8	4.3	2.0
5	3.2	1.6	5/16	4.4	1.9
2 1/2	3.5	1.8	Control	4.1	2.1
1 1/4	4.0	2.0			

There was slight inhibitory activity above 2.5 per cent. In testing Merck's maltose 5 c.c. of a 1 per cent. pepsin solution was employed. The following is a typical series:

Per cent.		Per cent.	
40	0.0	1 1/4	2.5
10	2.4	5/8	2.4
5	2.4	Control	2.5
2 1/2	2.6		

Maltose, therefore, in dilutions of 10 per cent. or less has no inhibitory activity.

Lactose gave the following result with 1 c.c. of 1 per cent. pepsin solution:

Per cent.		Per cent.	
supersaturated	0.9	5	1.7
20	1.1	Control	1.8

On the whole the inhibitory activity of the carbohydrates is slight and not apparent in solutions of a strength likely to occur in the stomach contents.

The hydrocarbons were difficult to test. The method was that employed by Pick, olive oil being added to various solutions of pepsin and filtered gastric contents. Of course, the oil did not mix with the solution but remained floating on the surface, and, as was to be expected, no inhibition was manifest. As Pick has shown that acacia has a strong inhibitory action it was not feasible to make emulsions.

Alcohol was tested with 5 c.c. of a 1 per cent. pepsin solution. A number of series were made, the results being practically identical. As, however, the percentage limits in the different series were not always the same we have combined them.

Per cent.		Per cent.	
64	0.0	2	4.4
32	0.0	1	4.6
16	1.5	½	4.6
8	3.6	Control	4.3
4	4.2		

Complete inhibition, therefore, at 32 per cent.; slight at 16 per cent.; and little or no inhibition in mixtures lower than 8 per cent.

Conclusions of First Section. The results of the studies of the inhibition by food and the products of its digestion may be briefly summarized.

Albumin produces no inhibition during digestion.

Albumoses have a strong inhibitory effect. Under normal conditions this inhibition probably is not active in the stomach. Under abnormal conditions, particularly in cases of retention, it may be a serious factor.

Gelatin has a distinct inhibitory effect.

Of the sugars, maltose appears to exert the strongest inhibition, and lactose none at all. It is not probable that this inhibition ordinarily plays a very important role in gastric digestion.

Hydrocarbons apparently do not inhibit; at least, when they are added to the gastric contents.

In view of these results it seems reasonable to conclude that some factor other than the food interferes with the gastric digestion. That it cannot be deficient secretion of pepsin, seems clear from the fact that dilution of the gastric contents outside the body gets rid entirely of the inhibitory factor or factors. It is possible either that some factor is present which prevents activation of the pepsinogen or that some substance is lacking which is necessary to

its activation. The question, however, is complicated. It is difficult to devise experiments which give decisive results; nevertheless, it seems capable of solution.

II.

The second part of our paper is concerned with the effect of various antiseptics employed in the preservation of foodstuffs. The controversy excited by the use of these substances has been exceedingly bitter, and, as is usually the case, experts have testified for both sides. In testing the effect of these preservatives reliance has hitherto been placed chiefly upon the effect produced by feeding foodstuffs treated with them to human beings or even to the lower animals for a considerable period of time. In some cases, very careful studies have also been made of the urine in order to determine whether they irritate the kidneys during elimination. Only a few attempts have been made to study the direct effect of those preservatives upon the digestive processes, and yet this would seem the most obvious thing to do, and the disturbance of digestion a most likely source of injury. Our investigations must not be considered as more than preliminary. We have endeavored merely to show what are the limits of the inhibitory activity of the preservatives when dissolved in artificial gastric juice or gastric contents. Of course, the same errors that apply to the study of inhibition upon the natural products of digestion apply in this case. Nevertheless, if a substance entirely prevents the proteolytic activity of the pepsin under the favorable conditions of an incubator and twenty-four hours' exposure in the Stender dish, it will certainly be effective in the stomach; and substances that in exceedingly moderate dilutions (such as salicylic acid and sulphite of sodium) interfere with digestion in the incubator, will also interfere with digestion in the stomach. It must not be forgotten that the mere inhibition or non-inhibition of peptic activity does not exhaust the capacity for harm of a particular preservative. Nor has the present series of investigations indicated what effect these substances have upon the proteolytic activity of the pancreatic secretion. The materials used have been, wherever possible, chemically pure.

As a preservative common salt is used principally for meats, fish, and butter. In saturated solution in $\frac{n}{20}$ HCl, using 1 c.c. of 1 per cent. pepsin or 1 c.c. of gastric contents as a digestant, a trace of digestion occurred when a saturated solution was diluted to one-eighth. The following results were obtained with known percentages:

1 : 20	Trace	1 : 160	1.7
1 : 40	0.8	Control	1.7
1 : 80	1.0		

Formaldehyde is used chiefly as a preservative for milk, or as a constituent in various preservative or embalming fluids. The dilutions were made with formalin, a 40 per cent. solution of formaldehyde, the active agent. Therefore, in order to obtain percentages of formaldehyde employed, the percentage or dilution that we give must be multiplied by 0.4. The following figures were obtained in different series of experiments:

1 : 10	0.0	1 : 80	1.7
1 : 20	0.0	1 : 160	3.0
1 : 40	0 6		

In this series the controls were unsatisfactory, and it merely indicates that absolute inhibition ceases between 1 to 20 and 1 to 40. In the second series the first column is with 5 c.c. of a 1 per cent. pepsin solution, and the second column is with 5 c.c. of filtered gastric contents of a total acidity of 75.

I.		II.	
1 : 100	2.0	1 : 100	0.9
1 : 200	2.6	1 : 200	1.2
1 : 400	2.7	1 : 400	1.2
1 : 800	2.9	1 : 800	1.3
1 : 1600	2.8	1 : 1600	1.5
Control	3.2	Control	1.5

Very doubtful inhibitory action in dilutions more than 1 to 100. In the beginning several series of tests were made in dilution of 1 to 1000 to 1 to 32,000, but no inhibitory effects were observed. We were rather surprised at the high concentration of formalin necessary to cause complete inhibition. These results agree with those of Bliss and Novy, who found that exposure to 4 per cent. formaldehyde did not destroy pepsin, but do not agree with those of Rideal and Fowlerton and Cassel, who found inhibitory activity. Starling believes that the formaldehyde prevents the digestion of fibrin that has been exposed to it, but has little effect upon the pepsin; perhaps an explanation of the different results.

Benzoic acid and benzoate of sodium are employed very extensively, particularly in preserves, pickles, catsup, etc. Benzoic acid dissolves very slightly in the HCl solution. In dilutions of 1 to 100 or higher the inhibition is absolute. In dilutions above 1 to 800 there appears to be no inhibition.

1 : 200	0 6	1 : 3200	4.0
1 : 400	1.5	1 : 6400	4.0
1 : 800	3.2	1 : 12800	4.1
1 : 1600	3.8		

Sodium benzoate in dilutions of 1 to 100 also causes complete inhibition. The following figures were obtained in a series of high dilutions, the digestant being 1 c.c. of 1 per cent. solution of pepsin.

1 : 200	1.6	1 : 800	2.4
1 : 400	2.0	Control	2.5

Boric acid is also extensively used. In supersaturated solutions it has no effect whatever upon the peptic digestion. This agrees with the results of Chittenden, Liebreich, and others.

Salicylic acid dissolves very slightly in the acid solution. As nearly as we could determine the saturated solution was about 1 to 500. The digestion was 5 c.c. of a 1 per cent. solution of pepsin. The results were as follows:

1 : 750	3.5	1 : 12000	5.0
1 : 1500	3.9	1 : 24000	6.1
1 : 3000	4.3	Control	7.3
1 : 6000	4.7		

With 1 c.c. of a 1 per cent. solution of pepsin the results were as follows:

1 : 200	0.8	1 : 20000	2.2
1 : 1000	2.0	1 : 40000	2.3
1 : 10000	2.1	Control	2.3

Sodium salicylate, when added to the HCl solution, is precipitated as crystals of salicylic acid, and the effects are probably the same. In all the dilutions which we employed there was total inhibition.

Sulphite of sodium is used in enormous quantities by butchers to restore the red color to the surface of meats that have been exposed to the air. In all dilutions lower than 1 to 100 it produced total inhibition. In the higher dilutions the results were as follows:

1 : 200	0.7	1 : 1600	3.4
1 : 400	2.0	1 : 3200	3.8
1 : 800	2.8	Control (average)	4.3

Even in dilutions as high as 1:1600, therefore, there is distinct trace of inhibition. It seems that this renders sodium sulphite particularly deleterious for employment upon meats.

Saltpetre (potassium nitrate) is another preservative frequently used. We did not determine the point at which it caused absolute inhibition. Solutions of 1 to 400 still showed slight inhibitory power.

Resorcin is not, as far as we know, used as a preservative, but was tested merely because of its extensive employment as an antifermentative and antiseptic in gastric conditions. The digestant was 1 c.c. of 1 per cent. solution of pepsin.

1 : 12	0.0	1 : 200	2.1
1 : 25	1.1	1 : 400	2.0
1 : 50	1.6	Control	2.2
1 : 100	1.6		

Inhibition ceases, therefore, if the dilution is in excess of 1 to 100.

Guaiacol carbonate is used for the same purpose as resorcin. It is almost completely insoluble in the HCl solution. The results were as follows:

Supersaturated solution	2.0	1/4 strength	2.3
Saturated solution filtered	2.2	1/8	2.3
1/2 strength	2.2	Control	2.2

Therefore, it has practically no inhibitory effect.

Creosote is also used as an antiseptic in gastric conditions and is one of the substances deposited in foods preserved by smoking. Creosote-water is prepared by mixing one part creosote to 100 parts water, agitating and filtering. The amount of creosote that goes into solution appears to be very small. We used $\frac{n}{20}$ HCl instead of water. The following figures were obtained, the digestant being 1 c.c. of a 1 per cent. pepsin solution:

Pure.	Trace.	1/8	1.6
1/2	0.6	1/16	1.9
1/4	1.0	Control	1.7

A few drops of creosote were added to 15 c.c. of the 1 per cent. solution of pepsin. There was a barely recognizable trace of digestion in the tubes.

Conclusions of Section II. Of the ordinary preservatives boric acid and borax may be regarded as without effect upon the peptic digestion.

Formaldehyde and alcohol appear to inhibit gastric digestion only when in high concentration.

Salicylic acid has a distinct inhibitory effect even in very high dilutions. This would seem to suggest that its reckless use may cause considerable impairment of nutrition.

Benzoic acid, sodium benzoate, and sodium sulphite inhibit very strongly gastric digestion.

Resorcin inhibits very slightly.

Creosote inhibits strongly, even in the high dilutions in which it is soluble in water or in acid solution.

On the other hand, carbonate of guaiacol, probably on account of its extreme insolubility in acid solutions, appears to have no inhibitory effect whatever.

III.

In the third section of the paper we report some experiments and investigations which had for their object the discovery of some method of diminishing the inhibitory activity of the gastric contents. It is certain that the inhibitory factor is destroyed by sufficient dilution, and that this dilution does not affect—excepting proportionately—peptic activity. Therefore, attempts were made to

determine the effect of dilution upon the digestive power of the stomach contents. The method employed was that of Mathieu and Rémond for the determination of the total quantity of the gastric contents. After the withdrawal of a test meal 300 c.c. of water were introduced into the stomach and mixed as thoroughly as possible with the remaining stomach contents. It was then withdrawn. By estimating the total acidity of the test meal and of the diluted test meal it was possible to determine just what fraction of the latter consisted of stomach contents; that is to say, supposing the total acidity of the test meal was 100, and of the diluted test meal was 20, the diluted test meal must consist of four parts of water and one part stomach contents. Theoretically, then, if the stomach contents were diluted to such a point that inhibition was overcome (that is 1 in 16), it should possess a digestive power compared with that of the diluted test meal (further diluted 1 to 16) equivalent to the square root of five, or, to state it more generally, equivalent to the square root of the filtered test meal. In a series of these test meals we obtained the following result

Case.	T. A.	Pure.	1/4	1/16
H. C.	90.0	2.2	2.5	1.6
Diluted	17.0	2.6	2.1	1 6
110	136.0	3.4	...	1.9
Diluted	42.0	1.4	2.5	1.1
124	90.0	0.8	4.8	
Diluted	19.0	0.6	3.4	
93	112.0	3.6	4.7	
Diluted	7.0	0.0	2.4	
151	70.0	6.7	4.5	
Diluted	5.5	1.0	2.5	
134	60.0	8.9	8.2	5.4
Diluted	8.6	2.8	4.6	3.3
97	66.0	9.0	7.9	5.2
Diluted	2.8	0.0	3.2	1.7
151	150.0	8.3	7.9	5.8
Diluted	13.5	4.1	4.4	3.0

In several cases the total acidity of the diluted portion was too low to permit digestion to proceed, and therefore the results were apparently negative. But in each instance it will be seen that when the acidity was restored by dilution (1 in 16) digestion became active. In no instance was the peptic activity of the diluted test meal (at a dilution of 1 in 16) as low as it should have been by the calculation, and in many instances it was almost as high as that of the test meal itself. There seems to be but two explanations: The introduction of the diluting fluid either stimulated the secretion of the pepsin, or else it converted some inactive form of pepsin into the active substance. In either case it caused a relatively great increase in the digestive power of the stomach contents. The therapeutic indication is not clear, but it would seem that the ingestion of large quantities of fluid in the late stage of digestion—that is

one or two hours after taking a meal—might considerably enhance the digestive activity of the stomach. Of course, it might have, in addition, some injurious effect either upon the motility of the stomach or upon the digestive activity of the intestine. Neither of these points has been determined.

These experiments are interesting from another point of view, that is, from the standpoint of the doctrine of antipepsin. This subject has already been discussed, but these experiments show conclusively, we think, that some factor other than merely concentration is present diminishing the activity of the gastric contents. Otherwise the dilution of the original test meal should, at some stage, give results strictly proportionate to a similar dilution of the diluted test meal, and this appears not to be the case.

If the mere ingestion of a considerable quantity of water can stimulate the production of active pepsin, there may be some method of stimulating the secretion of active pepsin in the gastric juice in cases in which it is ordinarily deficient or absent. In 1888, Jaworski called attention to the fact that in cases of achylia gastrica, if a dilute solution of HCl was introduced into the stomach and allowed to remain for an interval of time, pepsin could be demonstrated in practically all cases. This statement we attempted to verify. As a general thing the method employed was to withdraw the test meal, then to introduce from 200 to 500 c.c. of $\frac{n}{20}$ HCl, which was allowed to remain from fifteen to thirty minutes. The peptic activity of the test meal and of the HCl solution was then tested. Altogether we have had four cases of achylia gastrica in which repeated examinations had failed to show any trace of peptic activity, either in the pure or diluted stomach contents, and one case of carcinoma of the stomach, confirmed by operation, in which there was a distinct trace of peptic digestion, both in the stomach contents and in the HCl dilution.

Case.	T. A.	Pure.	1/4	1/16
99	22	0.0	...	0.0
200 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach	...	1.3	1.3	1.9
H. C.	...	0.0	0.0	0.0
500 c.c. $\frac{n}{20}$ HCl twenty minutes in stomach	...	1.2	...	0.5
54	20	0.0	0.0	0.0
300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach	50	0.0	1.5	...
H. C. (Carcinoma of stomach)	...	...	0.4	0.3
300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach	...	3.7	2.8	1.4
58	...	0.0	0.0	0.0
300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach	60	2.9	3.9	1.6

Whether the HCl serves merely to activate the pepsinogen, or also as a stimulant to its secretion, it is impossible to say. Presumably

the latter, because in several of these cases the amount of acid present in the gastric contents was sufficient to make digestion possible had there been any proteolytic ferment. The method, unfortunately, does not seem to be of value in distinguishing between carcinoma of the stomach and non-malignant achylia gastrica, although our investigations are still too few to enable us to speak with any certainty on this point. It does yield, however, a very distinct therapeutic indication, that is, that in cases of achylia gastrica the HCl should be administered *before*, and not after, meals. It should also be administered in sufficient strength and bulk to insure active stimulation of the gastric mucous membrane. Of three cases of achylia, all of which have received it in this manner, two have been greatly benefited; the third had been brought in a fairly good condition by several years' treatment before it was employed.

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ACUTE UNILATERAL SEPTIC PYELONEPHRITIS.

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During the past seven or eight years, surgeons have been greatly interested in a class of cases which had been previously regarded as beyond the scope of operative treatment. Up to 1899 one finds a few scattered reports of cases of acute unilateral pyelonephritis of the suppurative type which were operated upon. This condition was known as "surgical kidney" by our medical forefathers, because

it so frequently followed operations or manipulations upon the urethra or the bladder, or was a result of infection of the viscera which could be almost invariably found upon the autopsy table. With the introduction of aseptic methods in our operations upon the lower urinary passages the number of cases derived from this source diminished. It was observed, however, as a not infrequent complication of the cystitis accompanying calculus, enlarged prostate, and gonorrhea, although even at this time it was thought to be so uniformly bilateral that any operative relief for its symptoms was contraindicated.

Gradually the attention of the profession was drawn to the fact that acute symptoms of a septic character accompanied by localized tenderness, pain, and often palpable enlargement of the kidney, were due not only to infection ascending from the lower urinary passages, but that there were many cases which could not be thus explained. It was found that the organisms in the remaining cases must undoubtedly have been carried to the kidney through the circulation as metastases from distant foci of suppuration. The discovery thus was made and confirmed by a large number of surgeons that these septic lesions of the kidney, whether urogenous or hematogenous, were not only unilateral in the early stages, but that the cases with the severest septic symptoms yielded promptly to nephrotomy or nephrectomy.

One of the earliest writers to call attention to these unilateral septic renal conditions was Goodhart, in 1868. He found[1] at 130 autopsies upon cases of "surgical kidney" that the lesion was present upon one side in 14.5 per cent. In an additional 71 cases collected from the literature he found 12 (16 per cent.) unilateral. In 1883, Singer reported a case of unilateral renal suppuration immediately following typhoid fever. The kidney had been severely injured eighteen years before. One of the most interesting contributions to the literature of the subject is that of Robert F. Weir.[2] The case was one in which he performed nephrectomy in a young man, aged twenty-five years, who had a severe urethrocystitis three months previously. The chief symptoms were fever of a remittent type (to 105°) and chills. The colon bacillus was found in pure culture in the extirpated kidney.

In 1895, Woodward[3] reported a case in which he had performed nephrectomy for a unilateral septic nephritis. The first case reported herewith was published in August, 1899.[4] It is superfluous to mention in detail the articles that have been written since 1899. Excellent reviews of the entire subject have been published by Klink,[5] in 1903, and by Wagner,[6] in 1904. We now know that cases

[1] Guy's Hospital Reports, vol. xix.
[2] Medical Record, September 16, 1894.
[3] Annals of Surgery, 1895.
[4] Chicago Medical Recorder, August, 1899.
[5] Centralblatt der Mittheilungen aus den Grenzgebeiten der Medizin und Chirurgie, 1903.
[6] Schmdt's Jahrbucher, 1904.

of acute unilateral pyelonephritis with severe septic symptoms have a definite etiology and pathology, and that they can be recognized and are amenable to surgical treatment.

ETIOLOGY. The causes are best divided into the two chief modes of infection, urogenous and hematogenous.

1. *Urogenous Infection.* The various modes of origin of this form are:

(*a*) Cystitis. This is one of the most frequent causes of an ascending infection. The cystitis is usually of a chronic type and associated with retention of urine. For this reason the renal condition is more frequent in males, since the causes leading to stagnation and retention of urine are more frequent, owing to the presence of an enlarged prostate or of a stricture of the urethra. The acute pyelonephritis of pregnancy and of the puerperium, which is often so difficult to recognize, can be explained upon the basis of the cystitis frequently present and so greatly favored by the stagnation incident to these conditions.

(*b*) Hydronephrosis and nephrolithiasis. Both of these renal conditions favor infection of the parenchyma, through the obstruction to the outflow of urine which they cause, added to the microorganisms so often present in these conditions.

(*c*) Unclean ureteral catheterization.

(*d*) Ureteral fistulæ. Here there is no resistance to the transmission of infection to the kidney.

2. *Hematogenous Infection.* This arises as follows:

(*a*) As a complication of subcutaneous injury of the kidney. Israel called attention to this form of acute pyelonephritis in his text-book, in 1901, and George E. Brewer[7] has recently contributed some valuable clinical and experimental observations, eleven cases of his own, and two of Joseph A. Blake, of acute pyelonephritis. Eleven of these occurred in women and two in men. There was a distinct history of injury in two and previous disease in one. In five cases there was recent history of some febrile disorder. In order to confirm his view that an injury to a kidney is frequently followed by acute unilateral septic infarcts he bruised the kidney and injected hypodermically varying amounts of cultures of organisms, such as Staphylococcus pyogenes aureus, Streptococcus pyogenes, Bacillus coli communis, Bacillus typhosus, and Pneumococcus. Of sixteen animals which, in addition to the inoculation, received an injury to one kidney, five showed no lesion, or only hyperemia and parenchymatous degeneration. Two of these animals died within twenty-four hours of acute septic intoxication. Of the remaining eleven, all developed distinct surgical lesions of the kidney. In eight the lesions were unilateral, and limited to the injured kidney. In three, the lesions were bilateral. In one of the bilateral cases the

[7] Surgery, Gynecology, and Obstetrics, May, 1905.

lesions were practically equal in extent and in severity. In the other two, the lesions in the uninjured kidney were mild in character, and undoubtedly would have subsided under favorable conditions. The renal lesions produced by these experiments were practically identical with those observed in my clinical cases. They showed considerable variation in number, extent of renal destruction, and degree of resulting toxemia. While these experiments have not been sufficiently numerous nor varied to investigate all of the causes which might direct a given blood infection toward one kidney, they demonstrate in a very conclusive manner that injury to a single kidney, whether produced by trauma, the presence of a foreign body in the pelvis, or an acute obstruction of the ureter, certainly acts as a strong predisposing factor in the evolution of a surgical lesion of that organ.

(*b*) As a result of catarrhal conditions of the intestine or as a complication of stagnation of the fecal current. Baginsky and Heubner have called attention to the frequent occurrence of septic renal conditions due to the colon bacillus, as a metastasis of these organisms, following gastrointestinal disturbances in children.

(*c*) After the acute infectious diseases septic emboli are very likely to lodge in healthy and in hydronephrotic kidneys.

(*d*) As a metastasis from furuncles, tooth infection, or any form of peripheral suppuration. Hessert has recently reported a case of acute pyelonephritis following a carbuncle on the neck, and Israel has observed several such cases.

(*e*) As a metastasis from the lower urinary passages or from the opposite kidney in consequence of transmission of the organisms through the circulation, and not by means of an intervening ascending infection. This form is very prone to develop after urethral or vesical manipulation.

PATHOLOGY. The most satisfactory division of the various conditions in which the kidney is found either at autopsy or during life is that given by Israel.[8]

1. *Ascending Catarrhal Pyelonephritis.* In these cases the mucosa of the pelvis is swollen and there is marked catarrhal inflammation of the collecting tubules of the kidney.

2. *Multiple Miliary Foci of Suppuration.* This is the most frequent and typical form. The kidneys removed in both of my cases belong to this group. The small foci of suppuration are irregularly scattered through the entire kidney, the cortex being especially involved. The foci, as in my second case, may be almost exclusively confined to one pole of the kidney. The cortical foci project usually above the level of the surrounding parenchyma. They are usually arranged in groups, each abscess being surrounded by a zone of intense hyperemia. On section one sees many streaks of purulent softening extending from the hilum to the cortex and radiating in a fan-like manner from the pelvis.

[8] Nierenchirurgie, 1901.

3. *Hyperacute Form.* The course of the disease is so rapid that there is no time for the formation of foci. Examination of such kidneys shows only most intense congestion. At times there are some ecchymoses and turbidity. The entire cut surface is œdematous.

4. *A Few Large Abscesses.* This form is rare.

5. *Gangrene of the Pelvis and Gangrenous Foci in the Parenchyma.* This variety is very rare and its etiology unknown, but it is probably hematogenous.

A perinephritic abscess may result from the second, fourth, and fifth forms.

The organisms which may produce this condition are the Bacillus coli communis, Gonococcus, Staphylococcus aureus and albus, and Streptococcus pyogenes. According to Rovsing any urine-decomposing organism can cause the disease. At times it may occur during the course of a chronic pyelitis of hematogenous origin, or as a complication of tuberculosis of the kidney as a mixed infection.

Symptoms and Diagnosis. The symptoms vary according to the intensity of the infection. In general, one may speak of two classes of cases: The first class is the one in which the kidney is but little suspected to be the cause of the symptoms. In this variety the clinical picture is that of an acute, general septic intoxication. The principal symptoms are repeated chills, high temperature usually remittent, but sometimes continuous, rapid pulse, marked prostration, and nervous symptoms, such as restlessness, delirium, and stupor. There is usually marked leukocytosis. In all probability some cases which have been spoken of as cryptogenetic septicopyemia belong to this group, in which the general septic symptoms predominate. The local signs of a kidney infection are so slight that they are frequently overlooked, unless a very careful physical examination is made to exclude other causes of sepsis. These cases are often so acute in their onset (according to Brenner), and so rapidly progressive in their septic manifestations, that death may ensue before any renal or urinary changes show themselves. In the diagnosis the history of previous infection is of aid, as also that of some subcutaneous injury in the kidney region. The urine shows a few pus cells, or may contain nothing abnormal.

In the second class of cases the diagnosis is not so difficult, since the local signs predominate from the first and are accompanied by symptoms of septic intoxication. These local signs are: (*a*) Severe pain, most frequently located over the affected kidney. In the very acute cases this pain may not be so accurately localized, but referred only to the side of the abdomen corresponding to the affected kidney. When the right kidney is involved the differential diagnosis between this affection, appendicitis, gallstones, etc., is often very difficult. The onset is often as sudden as in any of the affections mentioned. (*b*) A second symptom of considerable importance

is marked tenderness on pressure in the costovertebral angle of the affected side. (c) A third valuable sign, well-marked in the second of my cases, is rigidity of the abdominal muscles in the neighborhood of the affected kidney. In some cases one can palpate the kidney as enlarged and extremely tender. This sign was of great value in my second case as a differential diagnostic sign serving to exclude other acute suppurative diseases of the right side of the abdomen. The urinary symptoms are decrease in quantity of urine and the presence of pus in variable quantity. The general symptoms are quite characteristic, and are similar to those observed in the class of cases in which the general septic symptoms predominate over the local inflammatory ones. Chills occur at frequent but irregular intervals and are followed by a marked elevation of temperature. The fever is usually of a remittent type, but may be continuous.

The most characteristic symptoms are: Location of the pain, tenderness, and rigidity over the affected kidney, accompanied by pyuria, chills, fever, and remittent temperature. Such a unilateral septic process may occur in a kidney which has been the seat of a previous chronic condition, such as calculus or tuberculous pyelitis. One of the local signs to be especially mentioned is the presence of severe renal colics. These are due, as Israel has shown, to the extreme congestion of the kidney. The colics may simulate stone to such an extent that they are accompanied by anuria. The differentiation can readily be made from the graver septic symptoms present in an acute unilateral septic nephritis. If such a septic process occurs in a displaced kidney the differential diagnosis is almost impossible.

The following two cases will serve to illustrate this form of acute unilateral septic nephritis:

Case I.—Mrs. B., aged twenty-six years, was admitted to St. Luke's Hospital June 4, 1898, on account of laceration of the perineum, cystitis, and suspected renal calculus. She stated that since the birth of her child (seven months previously) she had suffered from severe pain on urination, accompanied by the passage of calculi varying in size from a pea to a bean. Before the expulsion of these she had sharp pains in the region of both kidneys, with tenesmus and the passage of large clots of blood. There was intense burning and smarting on urination. The urine upon admission contained triple phosphates, pus, red blood corpuscles, and considerable albumin.

An exploratory nephrotomy performed in July, 1898, by Dr. W. H. Allport, resulted negatively. A little later the urethra was dilated, some small whitish particles were removed, and was followed by irrigation with silver nitrate. She was discharged on August 16, 1898, after her temperature had been normal for some time. The urine at this time contained a few pus cells; she still had incontinence, and occasionally passed pinhead-sized phosphatic calculi.

On August 24, 1898, she was readmitted, with a temperature of

105.4° F., and a pulse of 140. She stated that for the preceding four days she had suffered from excruciating pains in the region of the left kidney, which radiated down the ureter to the bladder and were accompanied by repeated chills and high fever. Examination revealed marked tenderness over the left kidney and very marked muscular rigidity in its vicinity. The urine contained a large number of pus corpuscles.

The diagnosis being made of pyonephrosis with probable renal calculus, I immediately performed an exploratory operation. The kidney was found adherent and greatly enlarged. Upon being brought into the abdominal wound, the many groups of miliary abscesses with hyperemic zones so characteristic of an acute pyelonephritis were seen scattered diffusely over the cortex. Nephrectomy was performed. Upon the following day the patient's temperature rose to 105°, and the urine was much clearer. The amount passed in twenty-four hours was 800 c.c. Upon the third day after operation she was removed to the isolated ward, on account of a faucial diphtheria; here she received 2000 units of antitoxin.

On her return to the surgical ward, on September 24, 1898, her temperature was normal; in twenty-four hours she passed 660 c.c. of urine containing pus and a few granular casts. The extirpated kidney showed many groups of miliary abscesses in the cortex, especially just beneath the capsule. On section yellowish streaks of purulent softening were seen extending from the apices of the pyramids toward the capsule. There were no calculi, but the pelvis was deeply congested and filled with pus.

The patient was operated upon after this twice during the next year: once for an ovarian cyst, and a second time for chronic recurring appendicitis. The latter operation was performed by myself. At this time (August, 1899), one year after the nephrectomy, her urine contained no pus; she suffered from incontinence during the day, but not at night. She passed from 46 to 48 ounces in twenty-four hours, and had gained twenty-two pounds in weight.

Case II.—Fred J. was seen in consultation with Dr. H. L. Baker, on October 27, 1905. He stated that about eighteen months previously he had been struck in the back with some degree of violence by a street car. He never felt well since that time, but had no definite symptoms, until about six weeks before my first seeing him. During this period he had severe pain in the back, fever, and chills. The cycles of recurrent chills and fever would last about a week; that is, he would have chills for a day, then high temperature, which gradually diminished, until at the end of four or five days he felt much improved. Then the chills and fever recurred. While in the hospital his temperature dropped from 104° to normal in three days. After being normal for twenty-four hours it suddenly rose to 104° again. There was marked rigidity of the abdominal muscles over the right kidney. The latter could be felt as enlarged and

very tender on bimanual examination. The urine contained a large amount of pus and was alkaline in reaction.

The patient refused operation until November 2, 1905, when the temperature after having been normal for twenty-four hours rose to 104° and was again accompanied by very rapid pulse and great prostration. I made an incision over the right lumbar region parallel to the last rib. On exposing the kidney many adhesions were found. The organ itself was brought to the surface. The cortex of the upper half was seen to be studded with a very large number of miliary abscesses arranged in groups with a hyperemic zone. A few were also seen over the lower half. Nephrectomy was done.

The temperature became normal after the operation. The urine for first few days contained small amount of pus. Since then it has been clear. He began to resume active work as a painter about six weeks after the operation. He has gained thirty pounds in weight.

I believe that in the first case the infection was urogenous from a marked cystitis. In the second case a possible injury to the kidney preceded the urinary symptoms by over a year. There were no signs of cystitis before or after the operation, so that the infection may have been hematogenous.

TREATMENT. There are three distinct methods of treatment. The first is the medical, which may succeed in the milder cases: the administration of urinary antiseptics and the ingestion of large quantities of bland fluids, such as milk, water, etc. The temperature should be controlled, as far as possible, by hydrotherapeutic methods. The bladder should be irrigated at regular intervals with weak nitrate of silver. Ureteral catheterization should never be used because of the danger of infection.

The other two methods of treatment are of an operative nature and differ only in degree. The first is nephrotomy, and consists of exposing the kidney and opening the multiple abscesses with or without stripping off the capsule. There are many surgeons (like Israel, Brewer, Johnson, etc.) who claim that this method does not give as good results as nephrectomy. Some of the more radical advocates of nephrotomy even recommend the excision of the affected areas, if this be possible, in order to conserve as much of the kidney as can be saved. Nephrectomy has almost as many supporters as the more conservative operation. Johnson cured only one of seven patients by nephrotomy, the remainder being discharged with fistulæ. In a later series of five cases he performed nephrectomy three times successfully.

Which one of these two operations is to be performed in an individual case rests to a great extent on the experience of the operator. In my own two cases nephrectomy resulted favorably in both, but I believe that in any future case I should be inclined to give nephrotomy a trial, especially if the disease was not far advanced and the areas of suppuration were miliary in size or only slightly larger.

I have been able to collect from the literature 34 cases in which nephrotomy was performed with 28 recoveries (82 per cent.), and 27 cases of nephrectomy with 25 recoveries (92 per cent.). It is, of course, unfair to draw conclusions from these statistics, since the cases vary greatly in severity. If the condition occurs during pregnancy conservative operation is indicated. If the condition is a part of a general pyemia extirpation of the kidney is out of the question.

GASTRIC ULCER IN CHILDHOOD.

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The following case of hematemesis occurring in a child of eight years has been of considerable interest, on account of its apparent rarity, and caused me to study the subject of gastric ulcer in childhood:

B. L., white, female, has been attending school, and living under excellent conditions of sanitation and nutrition. The family history is negative. The child was breast-fed, and well nourished in infancy. At the age of two years she had a rather severe attack of acute gastritis attended with fever and persistent vomiting for several days. She also had German measles, but otherwise none of the infectious diseases of childhood. For several years she has been "taking cold" easily, having several attacks of bronchitis every winter.

Her present trouble is of about ten weeks' duration. She suffers with repeated attacks of pain in the epigastric region. The pain occurs in paroxysms both before and after meals. Often it begins before meals, is relieved for a short time by taking food, and then returns sharper than before. It persists then a varying time, from one to three hours. At times it comes on in the midst of a meal. Sometimes it disappears quite suddenly. While in my office on the first examination she suddenly became nauseated and vomited, without apparent effort, food streaked with blood. The vomited matter gave the reaction for free hydrochloric acid. One week later, during an attack of pain, she again became nauseated and vomited about an ounce of bright blood.

The patient is rather frail and pallid. She weighs 42 pounds. The lungs and heart are normal. There is marked tenderness to pressure in the epigastrium. The stomach area is normal on percussion. The liver dulness is normal. The spleen is not palpable. There is no tenderness over the rest of the abdomen.

Examination of the blood revealed hemoglobin, 72 per cent. (Gowers); red cells, 4,200,000; whites, 8200. The urine was normal. The stools after the first appearance of blood in the vomit showed blood with the turpentine-guaiac test. After the second appearance occult hemorrhage persisted for four days. Subsequent examinations failed to show its presence.

The patient was put to bed on a five weeks' ulcer cure. All food was withheld for thirty-six hours, after which diluted milk and bismuth were given. The stomach symptoms disappeared after the first three days, and remained absent during the entire course of treatment. Since then, a period of five months, the child has been free from symptoms and has gained steadily in weight.

From the symptoms, the attacks of gastralgia, epigastric tenderness, hematemesis, the presence of blood in the stools, and the result of treatment, the diagnosis of ulcer of the stomach is, I think, justifiable.

A study of the postmortem statistics shows that ulcer in children is absolutely and relatively of uncommon occurrence, as compared with its incidence in adults. Thus, in Welch's[1] collection of 607 cases of gastric ulcer, but one occurred in a child less than ten years of age. Lebert[2] found but one case in his series of 226. By Rehn[3] we are told that Rokitansky never encountered a case under fourteen years, and was himself, in 1873, able to collect but 9 cases in children. Fenwick[4] collected 18 cases, and Cutler[5] in 1904 added 11 cases. It must be remembered that these statistics have been gained largely from hospitals where postmortem examinations on children are comparatively infrequent. An examination of the statistics of children's hospitals shows a somewhat different result. Dusser[6] found ulcer in the stomach in 9 cases; and ulcer of the duodenum in 4. In 390 autopsies at the Babys' Hospital in New York, Martha Wollenstein[7] found 5 cases of gastric ulcer. Holt[8] reports 3 cases accompanying follicular gastritis and 5 accompanying general tuberculosis. In order to obtain data as to its occurrence clinically, besides consulting the text-books on diseases of children, I wrote to the leading pediatrists of this country, with the following results: Booker, Rotch, Griffith, Louis Starr, and Koplik have never seen a case that they recognized clinically. Koplik[9] reports one case seen at autopsy accompanying empyema, which he states represents his experience covering fully 300,000 cases of diseases in children.

[1] Pepper's System of Medicine.
[2] Krankheiten d. Magens, 1878.
[3] Jahrb. f. Kinderheilkunde, 1873, p. 19.
[4] Disorders of Digestion in Infancy and Childhood, London, 1897.
[5] Transactions Amer. Gastroenterolog. Soc., 1904.
[6] Thèse de Paris, 1890. Cited by Holt, Diseases of Children.
[7] Cited from Osler, Practice of Medicine.
[8] Diseases of Children and Personal Communication.
[9] Ibid.

Jacobi,[10] on the other hand, states that it is not quite uncommon in children from seven to thirteen years. From the statistics of the children's hospital it appears that it occurs oftener than it is recognized clinically.

VARIETIES OF ULCERATION. Fenwick recognizes five varities of gastric ulcer: (1) Hemorrhagic erosions, (2) follicular ulceration, (3) tuberculous ulcers, (4) malignant ulcers, and (5) simple ulcer. The last may be either acute or chronic.

(1) *Hemorrhagic extravasations* into the gastric mucosa are frequently noted in children, as in adults. They are observed as the result of congestion of the vessels of the mucosa, secondary to uncompensated valvular disease or to dilated heart, complicating chronic pulmonary trouble, or more rarely in cirrhosis of the liver. They have also been seen in the hemorrhagic diseases, as purpura, scurvy, leukemia, hemophilia, and in jaundice. The hemorrhages vary from minute points, barely detectable by the naked eye, to irregular oval or linear areas. The smaller are limited to the mucosa, while the larger effusions may involve all the coats. This condition is of pathological rather than clinical interest. As will be seen later, Kundrat[11] considers the true ulcers to have their origin in the necrosis of the hemorrhagic areas.

(2) *Follicular ulceration* occurs for the most part in infants as the result of follicular gastritis. According to Fenwick: "Here and there small hemispherical masses about the size of a pin's head may be observed upon the surface of the mucous membrane. These appearances are due to inflammation of the solitary lymph glands situated in the wall of the stomach, and it is from the necrosis of these structures that the ulcers are produced. The swollen gland presses upon the gastric tubules which surround and cover it in, and gradually causes destruction of those in the immediate vicinity. A minute abscess is formed which opens on the surface." The disease seldom extends deeper than the submucous coat, but occasionally the muscular and the serous coats become involved.

According to Holt, these ulcers give rise to no symptoms other than those of the attendant gastritis, as a rule; he has, however, seen three fatal cases from hemorrhage occurring in young infants. The ulcers in these cases resembled those found in the intestines in follicular enteritis.

(3) *Tuberculous Ulcers.* Ulceration of the stomach due to tubercle is apparently less rare in children than in adults. Steiner and Neureutter met with 4 cases in 302 autopsies on tuberculous children. Widerhofer noted it twice in 418 cases, while Holt reports 5 cases in 119 autopsies in tuberculous children, but states that there is no positive evidence that the ulcers were the result of

[10] Diseases of Children.
[11] Gerhardt's Handbuch der Kinderkrank., 1880.

tubercle. Together this is a total of 11 cases of ulcer in 839 cases, as against Durk's[12] findings of but 4 cases in 900 autopsies on tuberculous subjects.

(4) *Malignant ulcer*, or rather the occurrence of carcinoma on the basis of a gastric ulcer in childhood, is unknown.

(5) *True peptic ulcer* in children is either acute or chronic. Morphologically they do not differ essentially from those seen in adults. Kundrat states that recent ulcers differ from those in adults only in that they are not always round, varying from a hempseed to a lentil in size. Their pathogenesis is as little definitely understood as in adults, though certain of the causes which are given to explain their occurrence can hardly be accepted as operable in children; such as hyperacidity and degeneration of the bloodvessels of the mucosa. Kundrat considered them the result of hemorrhagic effusions in the mucosa, destroying its vitality and permitting autodigestion by the gastric juice. He says: "If, as is commonly considered, hemorrhagic infiltration is the cause of hemorrhagic erosions, then for ulcus rotundum the same cause must be accepted. The difference between them is quantitative only and not qualitative. In the former case only the mucosa is affected, while in the latter the gastric juice acts also upon the submucosa and muscular layers." In support of this view may be cited the fact that hemorrhagic erosions and true ulcers are often found together in the same stomach. Ewald[13] inclines to this for at least a portion of the cases. Gerlardt[14] furnishes examples of erosions changed into true ulcers.

It is difficult to explain the occurrence of ulcers in the first few days of life on any basis other than that during parturition a hemorrhage into the mucosa has taken place and been followed by autodigestion. An infectious origin in children is indicated by the occurrence of gastric ulcer in children dying of tuberculosis, typhoid fever, pneumonia, noma, diphtheria, and empyema (2 cases). Ewald looks upon the bacteria as causal in a mechanical rather than toxic manner. He cites the observations of Nauwerk, Letulle, Dieulafoy, Stokes, and Kraft, who found emboli consisting of masses of bacteria closing up the smallest vessels of the mucosa. These are supposed to give rise to circumscribed disturbances in the nutrition of the mucosa followed by necrosis.

One acute case was evidently of traumatic or infectious origin following severe burns of the arms and legs.

Site of the Ulceration. With the addition to Cutler's statistics of several recent cases in which histories could be obtained, acute ulcers are found as often at the cardia as at the pylorus. They were midway between the two openings in two, and generally dis-

[12] Cited from Hemmeter's Diseases of the Stomach.
[13] Deutsche Klinik, p. 459.
[14] Virchow's Archiv., Band cxxvii, p. 85.

tributed in two. In chronic cases there appears also to be no special predilection of site. Multiple ulcers widely separated are frequent.

SYMPTOMS. These have been obtained from only some of the cases, the reports being inaccessible in some cases and deficient in others. In infants gastric symptoms are as a rule absent, indefinite, or masked by those of an infectious disease, a sudden hemorrhage, or pain from perforation, being the first evidence of the presence of ulcer. In a number of cases the ulceration was an unexpected pathological finding. In older children the symptoms are similar to those in adults, but seem to be milder. Excepting immediately preceding perforation, in but one case was the pain severe.

Pain and tenderness were noted in but 13 per cent. of the acute cases; but were present in over 60 per cent. of the chronic cases. The pain was usually not severe. In those cases in which the patients were able to impart information, it was localized in the epigastrium. In young children it seemed over the entire abdomen. In all cases it came on in paroxysms, occasionally before, but more usually after meals, and was relieved by vomiting. Intense pain was followed by hematemesis or perforation.

Vomiting. In the acute cases in infants, vomiting was usually subsequent to diarrhœa. In older children it followed epigastric pain and relieved the distress. In cases accompanying follicular gastritis, vomiting was persistent. Fenwick mentions the finding of minute pieces of mucous membrane in the vomit in cases of gastric erosions.

Hematemesis was noted in 40 per cent. of the cases in which histories were obtained. It was bright red and varied from a few streaks in the vomited material to a quart(?). In 4 acute cases it was the immediate cause of death; the stomachs were found filled with blood. In chronic cases the hematemesis was preceded by epigastric pain. In the acute, pain was often absent.

Symptoms of Indigestion. Anorexia, fulness, and distension, nausea, or heartburn were seldom complained of. Excepting acute cases, they were noted only in the chronic cases.

Stools. Diarrhœa was a prominent symptom, being present in almost one-half the acute cases. It usually preceded vomiting. Constipation was at times followed by diarrhœa. Melena was noted in the majority of cases of hematemesis. I have not been able to find a case in which it completely replaced hematemesis, although it is mentioned as a possibility, by Fenwick. Occult bleeding was, with the exception of my case, not noted.

Fever was noted in a considerable number of cases, running in infants as high as 106°. Cutler reports a temperature of 102° in a girl of six years and 101° in a child of eight.

Blood examinations were made in but 2 cases. Both were

anemic. Hemoglobin, 75 per cent., and 60 to 85 per cent. In one the leukocyte count was normal; in the other, 25,000 to 27,000.

COMPLICATIONS. A striking feature of acute ulcer in children is the large percentage of *perforations*. In 18 cases in which autopsies were made perforation was found in 6, or 33 per cent. In 8 fatal cases of chronic ulcer it was present in 3, making a total of 9 cases of perforation in 26 fatal cases. The symptoms are sharp, sudden pain in the abdomen, vomiting and collapse. Death occurs within thirty-six hours. This complication is not infrequently the first indication of ulcer. In older children, symptoms of the complicating peritonitis are sometimes seen, as in adults; but in young children collapse with rapidly fatal termination is the rule. Bisset has recently reported a case of perforation in which the initial symptom was profuse hemorrhage. In 1 case, perforation of the diaphragm occurred with subsequent pyopneumothorax. In Chvotek's[15] case stenosis of the pylorus and dilatation of the stomach is recorded. The base of an ulcer had formed adhesions with the pancreas, and contracted narrowing the pylorus so that it would hardly admit the tip of the little finger. Krasnobayeff,[16] reports 3 cases of stricture of the pylorus in children.

Robinson[17] reports a case of chronic ulcer in a boy of fourteen years, in whom autopsy showed two strictures of the œsophagus with a diverticulum. The stomach was markedly contracted in size and the pylorus thickened and constricted. At the pylorus was a large ulcer almost encircling it. The mucosa was replaced by fibrous tissue to which the contracture of the stomach was probably due.

DIAGNOSIS. In those cases in early infancy in which the first symptoms are profuse hemorrhage or collapse from perforation, early recognition is obviously impossible. In older children the symptoms are usually so little distinctive, and the disease of such uncommon occurrence that the diagnosis must depend largely on the finding of blood in the vomit and stool. And here care must be taken to eliminate the many other causes of hematemesis and melena. Thus in Dusser's 24 cases of hemorrhage from the stomach and intestines, in only 13 was ulcer found. In infants the blood may rise from the gums, nose, throat, or lungs, and be swallowed, followed by vomiting. Blood may be sucked from the breasts of the mother, or, in neonats, have been swallowed during parturition. True hematemesis arises from a number of causes other than ulcer. It has been observed in purpura, hemophilia, scurvy, and similar diseases in which there is a tendency to bleeding from any of the tracts. Cirrhosis of the liver, a not very uncommon condition in children, may give rise to

[15] Archiv. f. Kinderheilkunde, 1882, vol. iii, p. 267.
[16] Dietsh. Moskau, 1898, iii, p. 195.
[17] International Clinics, 1905, 15, s. iii, p. 119.

it. In malignant forms of the exanthemata, notably measles and variola, it is likely to occur. I have seen it in a case of influenza. Other causes are: corrosive poisoning, severe retching (as may occur in pertussis), and traumatism as due to swallowing of foreign bodies. The great majority of these can be eliminated with a little care. In cases of melena the elimination of other causes presents greater difficulties. It is present in practically all cases of hematemesis, either as visible or occult hemorrhage. The importance of its recognition lies in the possibility of it completely replacing the vomiting of blood. In addition to the causes already mentioned as producing hematemesis, the possibility of intestinal origin must be considered. These are ulceration of the bowel due to catarrhal enteritis or colitis, tuberculosis, and typhoid fever; further, intussusception, thrombosis of the mesenteric artery, intestinal parasites, rectal polyps, hemorrhoids, and straining at stool. In neonats, melena frequently occurs without discoverable cause.

It is not unlikely that, with the attention now being devoted to the recognition of occult hemorrhage, curable ulcer of the stomach will be more frequently recognized in children suffering with chronic stomach disorders.

REVIEWS.

DIET AND DIETETICS. By A. GAUTIER, M.D., of Paris, France. Translated by A. J. RICE-OXLEY, M.A., M.D. Pp. 552. London: Archibald Constable & Co. Philadelphia and London: J. B. Lippincott Co., 1906.

DIET IN HEALTH AND DISEASE. By JULIUS FRIEDENWALD, M.D., Clinical Professor of Diseases of the Stomach in the College of Physicians and Surgeons, Baltimore, and JOHN RUHRÄH, M.D., Clinical Professor of Diseases of Children in the College of Physicians and Surgeons, Baltimore. Second edition. Pp. 728. Philadelphia and London: W. B. Saunders Co., 1906.

EATING TO LIVE, WITH SOME ADVICE TO THE GOUTY, THE RHEUMATIC, AND THE DIABETIC. By JOHN JANVIER BLACK, M.D., Fellow of the College of Physicians of Philadelphia. Pp. 412. Philadelphia and London: J. B. Lippincott Co., 1906.

THE striking advances that have been made in our knowledge of the physiology of the alimentary canal in the past few years have stimulated general interest in dietetics and the treatment of disease by means of diet. This revival in the attention paid to alimentary physiology, coming as it does at a time when the general tendency of therapeutics is toward treatment by physiological measures rather than by drugs, has brought the whole subject of dietetics and alimentation into considerable prominence. Medical literature is as yet scantily supplied with works upon diet which are available for reference by the general practitioner, and it is with pleasure that we note the appearance of the volumes which are the subject of this review.

The books differ somewhat in their scope and character. Gautier's is characterized by its thorough presentation of the physiology of alimentation and the chemical and physical characteristics of different foods. Instead of furnishing arbitrary diet lists for each condition, he helps us to apply physiological principles to the diet of the individual patient. His consideration of diet in disease is brief and forms a comparatively inconspicuous portion of the book, but it is none the less admirable on this account. The first division of the book includes the physiology of digestion and of assimilation,

as far as our limited knowledge will allow us to go. The question of the optimum amount of the different constituents of our food is considered in a manner that appears to us to be as satisfactory as is possible at this time. Gautier warns us against theoretical feeding, even if the principles upon which it is done appear perfectly rational. He says that the proteid and ternary optimums should be determined rather by the experience of the race than by chemical analysis—a statement which will meet the hearty support of most clinicians. The best proportions of the three main constituents of diet are most determined, according to Gautier, by studying the diet that accurately maintains a race at the highest point of intellectual and physical vigor. To do this, the analysis must include as large a number of individuals for as long a time as possible and must include all classes of society. Gautier does this by analyzing the diet of the three million inhabitants of Paris for ten years. For his conclusions we must refer the reader to the book.

Next, the physiology of digestion is considered, including a satisfactory review of Pawlow's work, especially the influence of the mind upon digestion. Then the principles of the realization of energy from food, experimental calormetry, and Atwater's respiratory chamber are fully described. The application of these principles in determining the indispensable minimum of proteid and ternary food is then considered. As we have inferred, Gautier opposes the idea that the indispensable minimum corresponds to the diet best suited for obtaining the highest development of the race. He shows quite clearly that such a minimum is fitted only for individuals in a condition of physical and intellectual inactivity. He then compares this diet with the ration chosen by workmen of different sorts in different conditions.

In the second part, the chemical and physical characteristics of different foods are well considered in a very practical manner. The food values of different articles of diet are clearly given, and the section is well suited for easy reference. A detailed description of this part of the book is impossible; but we note with pleasure the sections upon the value of broth as food, upon preserved foods, milk and its derivatives, eggs, cereals, and a full consideration of vegetable foods. Under the head of nervine aliments are included coffee, tea, and cocoa. Alcoholic beverages and alcoholism are given considerable space. Then follows a chapter upon condiments and inorganic foods, in which iron, the alkalies, phosphorus, etc., are considered. A series of chapters is devoted to drinking waters, and includes waters of the different spas, disease attributable to drinking water, and filtration. Part II closes with sections upon the preparation of food and arrangement of meals, both as to time and composition.

In the third main division are given the regimens best suited to various methods of living, classes of society, kinds of work, seasons,

age, etc. A very moderate section upon vegetarianism points out the fallacies in the theories of the extreme supporters of such a dietary.

The diet in illness is then considered. As we have said, this does not form a prominent portion of the book, although its brevity detracts nothing from its importance. In it, Gautier briefly applies the principles that he has explained. Of course, unless one has been interested in what has gone before and has mastered the principles of alimentation, as far as we know them, this part of the book seems inadequate. It certainly contains no arbitrary diet list for different diseases, but in spite of this, indeed because of it, these chapters impress us as a very rational treatment of dietary in disease and a very fitting termination to a scientific and broad consideration of the whole subject of diet.

The translation by Dr. Rice-Oxley is decidedly above the average and is entirely adequate, with the exception of a few paragraphs.

In Friedenwald and Ruhräh's book the diet in disease occupies a much more prominent position. The principles upon which dietetics rest are not neglected, however, for the chapters upon the chemistry and physiology of digestion are very well done, although somewhat brief and condensed. The first edition of the book has already been reviewed in this department, so that a detailed reference to its contents is unnecessary; but for the purpose of comparison it may be well to speak in a general way of the authors' presentation of their subject. The chemical and physical properties of food, whether animal, vegetable, or inorganic, the consideration of water, mineral waters, coffee, tea, and alcoholic beverages, are all adequately considered. There are sections upon the preservation of food, artificial foods, preparation of food by cooking, infant feeding, and a diet for old age. This new edition also contains a more extended account of Prochowinck's diet for pregnancy complicated by contracted pelvis. The general consideration of dietetics closes with a concise, but very complete, account of rectal feeding.

The next 250 pages, comprising the bulk of the volume, consist of diet lists and regimens for different diseases. The authors do not confine themselves to the affections of the gastrointestinal tract, but consider the diet in practically all of the conditions treated by the internist and by the surgeon. The section upon disease, in which diet is a primary factor, includes diabetes, gout, obesity, under-nutrition, scurvy, and rheumatoid arthritis. We confess that we hardly see the propriety of including the last mentioned disease under this heading.

The last section of this book contains tables of army and navy rations, dietaries in public institutions, receipts, and rapid reference diet lists. These last dietaries are one of the best features of the

book, because they seem to represent more of the authors' own experience and opinions than the more elaborate lists in the body of the volume. The book is an admirable one and much needed by the practitioner in America. The form in which the scientific principles of alimentation are given is more popular and more concise than in Gautier's work, and on this account will probably appeal more favorably to the general practitioner, and the form of dietaries given will make the book a popular one for reference with the clinician. It appears to us that the book is open to criticism in one particular, namely: that it is too evidently a work of compilation. While an admirable summary of the literature of dietetics, we feel that the book would have been more valuable still if the authors had included in it more of their own personality and had given us the advantage of their own judgment and experience—which they are so abundantly qualified to do.

Dr. Black's book is avowedly popular. It consists of a rather informal discussion of dietetics in general, the value of different foodstuffs, and the author's strong support of Chittenden's well-known advocacy of the reduction of the amount of proteids in our diet. Indeed, as the title implies, the real reason for the book's existence is to urge moderation in eating along the lines that Chittenden has indicated. Dr. Black has woven into his text much of his own views and reminiscences, and consequently much of his own personality, which adds materially to the interest and attractiveness of the monograph. The book contains a general discussion of digestion and assimilation, the value of different foods and dietaries for consumption, obesity, under-nutrition, gout, rheumatism, and diabetes, but beyond this no diet lists are given. J. D. S.

A Text-book of Materia Medica, Therapeutics, and Pharmacology. By George F. Butler, Ph.G., M.D. Philadelphia and London: W. B. Saunders Co., 1906.

We are informed that the present (fifth) edition has been entirely remodelled, rewritten, and reset in order to keep abreast of the remarkable activity in the study of pharmacology which has marked the past four years. One of the most striking changes to be noted in recent text-books on therapeutics concerns the classification of drugs. No system of classification hitherto devised is altogether satisfactory, and the plan adopted in the present work of grouping the various drugs according to the system of the body on which they chiefly exert their action has, at least, the advantage of being

thoroughly practical. Some of the older subdivisions, such as antipyretics, analgesics, alteratives, astringents, and the like, have of course been retained, for obvious reasons. The question of classification, after all, has merely an academic interest and hardly deserves the enormous amount of thought and disquisition which has been expended upon it. Every practical requirement is satisfied if the book is provided with a table of contents, and a comprehensive general and clinical index, as is the case in the present instance.

In the introduction the author touches upon certain general questions that have an important bearing on the action of drugs and other remedial agents, and now form an integral part of our theories of disease and the process of recovery and return to normal condition. We say touched upon advisedly, as it seems to us that their treatment is too brief for a text-book on therapeutics. Where else indeed shall we look for satisfactory summaries of such questions as osmosis, electrolytic dissociation, and Ehrlich's side-chain theory of immunity? The literature on the subject consists chiefly of papers written for the investigator rather than for the general student, and requiring interpretation and even a certain amount of popularization before they can be assimilated and applied to practical medicine. This criticism might be thought unjust were it not that the author distinctly states in the preface that his book is intended essentially for students and practitioners, not for experimental workers in pharmacology. Nor do we agree with the author that much of the material which has been eliminated in the present edition from the chapter on serum-therapy belongs more properly to pathology. A thorough understanding of the theories of immunity is, in the present state of therapeutics, almost as essential to the practical doctor as to the laboratory worker, and the subject may very properly be included in text-books on practice and therapeutics.

On the other hand, matters of more immediate practical application, such as methods of administration, dosage, the secondary effects of drugs and the like receive full consideration in the introductory portion of the work. In the matter of dosage, unfortunately, we have not advanced beyond the stage of empiricism, and the practitioner is practically dependent on his own experience, and his knowledge of his patient's individual reaction to drugs in general, and to special medicines. The proper selection of the dose is usually more difficult than the choice of the drug itself, and this probably explains why the results obtained with the same agent differ so much in different hands.

The dose of digitalin is given as from $\frac{1}{100}$ to $\frac{1}{80}$ of a grain, although much higher doses are generally employed when a distinct effect is desired—as high as $\frac{1}{8}$ or even $\frac{1}{4}$ of a grain. It is also stated that digitalin is insoluble in water, whereas it can readily be dissolved in water for hypodermic administration. Aspirin, we are told, may be given in doses of 30 to 45 grains. The same dose

is mentioned by Cushny in his last edition, so that there is authority for such heroic doses. Personally, we have seen distinct salicysm produced in an adult by 10 grains, four times a day, on the second day of administration, not to mention the fact that in such large doses the drug is a decided irritant to the stomach. Several of the newer drugs which have recently come into general use and have proved their efficacy are not considered worthy of mention. However, a certain degree of conservatism is quite proper in a systematic text-book, and it is undoubtedly difficult, at this early date, to give a sound opinion on remedial agents, which must still be regarded as in the experimental stage.

A dozen pages are devoted to organo-therapy and serum-therapy. In spite of all the work that has been done recently in these two fields of therapeutics there is virtually nothing new that is of any practical value to be recorded. Diphtheria antitoxin is still the one serum of which it may be said that it has become a permanent part of the Pharmacopœia, with the possible exception of Pasteur's virus for the cure of rabies, the importance of which is limited only by the comparative rarity of the disease.

The arrangement of the subject-matter and the paragraphing of the book are excellent, and the author is to be congratulated on his success in presenting everything that is essential in a concise, summarized form. In its new edition the book will maintain the place it has already achieved among the standard current text-books. The clinical index is a very valuable and convenient addition.

R. M. G.

UNTERSUCHUNGEN UEBER AMINOSAUREN, POLYPEPTIDE, UND PROTEINE (STUDIES OF AMINOACIDS, POLYPEPTIDS, AND PROTEINS). By EMIL FISCHER. Berlin: Julius Springer, 1906.

THE CHEMISTRY OF THE PROTEIDS. By GUSTAV MANN. Based on Professor Otto Cohnheim's *Chemie der Eiweisskörper*. London: Macmillan & Co., Limited, 1906.

THE book by Fischer is a collection of the papers that have been written by himself and his co-workers upon this subject since 1899, preceded by a discussion, eighty-three pages in length, of the reason that these studies were undertaken, and the purpose that has been followed in them, together with a consideration of the chief results that have been obtained. The papers themselves and Fischer's preliminary discussion are all technical, and will be uninteresting and incomprehensible to persons that have not some knowledge of chemistry. To physiological chemists, however, and to students of nutrition,

they are of intense interest, since they furnish some of the most remarkable and important knowledge that has been contributed in many years. Our present knowledge of the nature of protein substances—that is, that they are constituted of groups of amino-acids bound together, in the case of the different proteins, in differing amounts—and the profound changes that this has made in our conceptions of digestion and nutrition in general are due, in large part, to the studies contained within this publication. In addition to this the work contains the studies on the formation of the polypeptids—substances that constitute the first approach to the synthetic production of protein. It was Fischer's reference to these substances in his paper before the German Chemical Society, the paper which opens this book, that led to such excited statements on the part of the lay press that he had practically made protoplasm and might be expected soon, perhaps, to make man—statements that he greatly deplores in a footnote, and that were clearly mere newspaper sensationalism. He expresses, on the contrary, in the original paper the attitude of the ideal scientist, when he states that it would be unfortunate if, by a mere lucky chance, someone should today light upon a method of artificially producing a true protein; for this would really contribute very little to chemistry or biology, and it would deprive scientists of the present fascinating opportunity to go on by slow and painful, but accurate, steps until, the whole matter having been carefully put together, protein will some day be produced in a manner that can be explained in each of its details.

As its title indicates, the book edited by Dr. Mann is, in most important particulars, practically an English edition of Cohnheim's well-known work. As the English editor explains, he takes the responsibility for this edition wholly to himself, because he has made certain modifications that are not in consonance with the views of Cohnheim, and thinks it more just to take this entirely upon his own shoulders. In many ways, however, the book has been put into a form quite different from Cohnheim's. On the whole, the author's reasons for not simply publishing a translation of Cohnheim's book, with notes by the editor, seem scarcely sufficiently forcible. He differs with Cohnheim chiefly in points of theory, and such differences anyone can excuse and can accept the theories of either at their proper value. The essential importance of the book lies in the fact that it is a very valuable discussion, which had not been attempted satisfactorily before Cohnheim did it, of the actual knowledge, rather than the theories, of the chemistry of the proteins. A very considerable part of the knowledge that is collected in the book is dependent upon the contributions of Fischer and his students, which have been reviewed under this same heading.

The book takes up the dissociation products, primary and secondary, of protein; the synthesis of albumins, a subject that is, as yet,

of course, extremely incomplete; and the carbohydrate, sulphur, and other radicals. There is then a discussion of albumoses and peptones; of the salts of the albumins; of the special reactions, combinations, and oxidation-products; of the general physical properties of albumins according to Cohnheim and according to the author; and also of the classification of albumins according to each of them. There is then a discussion of the chemistry of the albumins proper, the globulins, the vegetable albumins, and the various other substances included under the term protein.

To the worker in physiological chemistry and in disorders of nutrition the book is of great value, and such workers are deeply indebted to Cohnheim for first collecting the information that it contains and to Mann for presenting it in English form.

D. L. E.

AUTOINTOXICATION INTESTINALE. By DR. A. COMBE. Paris: J. B. Baillière et Fils, 1907.

IN discussing the question of autointoxication from the digestive tract, two main courses are open: one, a course that was followed for example in a most interesting way by Weintraud in a short article in Lubarsch and Ostertag's "Ergebnisse," is to consider the whole subject from a critical standpoint, and admit nothing as wholly acceptable under this heading except those conditions that have, with a considerable degree of scientific accuracy, been shown to be the result of autointoxication from the alimentary tract; admitting, of course, at the same time, that there are suggestive reasons for thinking that other disorders may be due to this cause. The other course is to accept, as many authors have done with a lively enthusiasm, all sorts of conditions as due to this cause, providing that there is the slightest indication that the gastrointestinal tract shows abnormality and that treatment of such abnormality causes improvement in the symptoms; and providing, also, that other evident reasons for these symptoms are not found.

The latter course has been followed by Prof. Combe; and, indeed, in some instances he goes even further than this, practically attributing some conditions that are almost certainly due to disturbance of the thyroid, for example, or of some other internal organ, to intoxication from the digestive tract, which, he would have us believe, secondarily produces the disorder that is commonly considered to be the causative one. The reviewer cannot at all agree with the correctness of this attitude.

The book is written in a very interesting way, taking up the manner in which the protein molecule is broken down in digestion,

the nutritive and toxic products of this process, and the experimental work that has been done in attempting to demonstrate the occurrence of intoxication in disorders of the digestive tract; then discussing at considerable length a large number of clinical conditions that the author attributes to intoxication from this cause; and reporting numerous studies of urine, etc., in support of his views. He finally devotes an extensive portion of the book to a detailed discussion of the dietetic and other treatment of such conditions.

This latter part of the book is the most valuable, and giving attention to the details recommended is likely to do good to many persons who have the various symptoms that the author describes; but enthusiasts about this matter overlook the fact that proper dietetic, hygienic, and other measures are likely to do good to persons with many disorders, whether their disturbance is primarily due to disease of the digestive tract, or to any one of a great number of other conditions, and whether it is toxic or nutritive. Consequently, the therapeutic test, while very valuable to the patient when successful, is not convincing evidence of the truth of a theory. One needs to accept some of the references in the work with caution, at least in the sense in which they are used; they have evidently been employed somewhat hastily to support the author's views and the form in which they are put does not always correspond with the actual views of the original authors. D. L. E.

LECTURES ON TROPICAL DISEASES. Being the Lane Lectures for 1905, delivered at the Cooper Medical College, San Francisco, Cal. By SIR PATRICK MANSON. Chicago: W. T. Keener & Co., 1905.

TROPICAL diseases in themselves are an interesting subject for study and an important one, at the present moment, for all Americans. In the Lane Lectures, which are the most delightful reading, the reasons for this importance are made perfectly clear, and the mode of transmission of certain tropical diseases from person to person, the spreading from country to country and continent to continent, is made easy of understanding. Besides these general considerations, the etiology, pathology, and symptomatology of several specific diseases are discussed in separate chapters: ankylostomiasis, dracontiasis, bilharziasis, trypanosomiasis, and several others. The author has been so closely associated with the study of these diseases that he speaks not only with authority but often from first experience. The book is altogether charming and one absorbs the really great amount of information which it contains in the pleasantest possible manner. W. T. L.

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The Diagnostic Value of Koch's Tuberculin.—ROTH-SCHULZ (*Beiträge zur Klin. der Tuberkulose*, 1906, vi, 167) gives the results of the use of tuberculin as a diagnostic agent in the Beelitz Sanatorium from 1902 to 1904. Over 1000 patients received the injections, nearly all being doubtful cases without lesions demonstrable by physical examination. The method employed is to administer as the initial doses 0.5 mg. of tuberculin after the temperature has been carefully observed for from four to seven days. Injections are undertaken only when the temperature is normal or shows a very slight elevation. If no reaction occurs after the first injection, in from two to four days, the same dose is usually repeated, particularly if any symptoms suggestive of a mild reaction have occurred with the first. If the temperature shows any irregularities, a longer period is allowed to elapse. Occasionally, the same small dose is repeated a third time, but, as a rule, at the next injection 1.25 mg. is given. If still no reaction occurs, this amount is occasionally repeated, but usually the dose is advanced to the maximum of 2.5 mg., which again is repeated once or even twice. A reaction is considered positive if the temperature rises 0.5° C. above the previous maximum, but the general and local phenomena are considered of great importance. The occurrence of rales where previously they were definitely absent or the occurrence of severe general symptoms are considered positive in spite of only a slight elevation of temperature. The importance of repeating the same dose of tuberculin is emphasized. Commonly a merely suggestive reaction upon the first administration

is followed by severe symptoms after the second. This curious feature is analogous to the hypersensitiveness which sometimes develops during diphtheria and tetanus immunization and, indeed, may occur upon the administration of various sera. In Roth-Schulz's series of cases there is no relation between the sex, age, or general condition of the patient and the degree of reaction to the drug. The male patients react as a rule to smaller doses than the female but no factor is discovered to explain this. The duration of a lesion and its acuteness apparently bear no relation to the intensity of the reaction. The slight, closed, early cases seem to react more readily than others. As to the specificity of the reaction, we must depend chiefly upon the reports of veterinarians, and these are now almost unanimously agreed that when a definite reaction occurs tuberculosis must be present. The more carefully autopsies are performed the lower the percentage appears of reactions without demonstrable tuberculous lesions. The frequent occurrence of marked reactions in apparently normal adults and the absence of tuberculin sensitiveness in the newly born corresponds, too, very closely with our knowledge of the occurrence of tuberculosis in man. The fact that so many apparently normal adults do react positively to tuberculin is the one objection to be raised to its use as a diagnostic agent. It would be foolish to employ it indiscriminately and treat, in a sanatorium, everyone who reacts. It is merely a link in our chain of evidence and the careful consideration of the accompanying symptoms, which render the patient a suspect, are of the greatest importance for diagnosis. Marked reactions to small doses are very suggestive of an active lesion.

Clinical Contribution to the Etiology and Pathogenesis of Hepatic Cirrhosis.—JAGIE (*Wien. klin. Woch.*, 1906, xix, 1058) reports a number of cases of cirrhosis of the liver which have been carefully observed during the past few years in the late Dr. Nothnagel's clinic. He points out the unsatisfactory classifications at present obtaining and insists upon the importance of discovering if possible the underlying cause of the condition. The anatomical classification, for instance, is a very unsatisfactory one, as alcohol, among other poisons, may cause two distinct types of the disease. In his first group of cases, numbering seventeen, the clinical picture is fairly uniform. All of them are marked alcoholics, and the initial symptoms of the disease those of alcoholic gastritis and enteritis. Jaundice occurs early in all, and is of a various and varying degree. One special symptom upon which Jagie lays great stress is the occurrence of attacks of pain in the hepatic area with tenderness over the liver. This he considers an important diagnostic feature. According to Naunyn, the attacks of pain and the jaundice are referable to an associated cholangitis. With every cirrhosis there is a certain degree of obstruction to the flow of bile, and this stasis must favor bacterial infection. Jagié points out that conversely infection from the catarrhal intestines may play an important etiological role in these cases. In the second group, numbering five cases, the importance of a chronic tuberculous lesion, as a causative factor, is strongly emphasized. A history of excessive alcoholic indulgence is absent; but all give a definite history of symptoms produced by tuberculosis, arrested apical lesions, pleurisy, protracted and severe bronchitis. The autopsy in all five cases,

too, showed old pulmonary, glandular, or bone tuberculosis which had, in all probability, antedated the cirrhosis. The clinical picture is quite different from the alcoholic cases. The attacks of hepatic pain and the jaundice are absent. Indeed, the symptoms of any liver derangement are so slight as scarcely to draw attention to the organ. The importance of tuberculosis as an etiological factor in cirrhosis of the liver is further emphasized by certain animal experiments. Bensancon and Griffin, by the injection of pus from cold abscess, and Bartel by the injection of tubercle bacilli of low virulence, have observed in guinea-pigs, changes in the liver identical with cirrhosis as it occurs in man. Other authors have obtained similar results. Hansemann describes a form of spontaneous tuberculosis in guinea-pigs regularly associated with cirrhosis of the liver and often accompanied by attacks of jaundice.

Mechanism of Compensation in Tricuspid Insufficiency.—FRANKE (*Wien. klin. Woch.*, 1906, xix, 956). Many clinicians, considering the anatomical arrangement of the circulation, have contended that no satisfactory compensation of a tricuspid lesion can be established, as there is no driving force back of the lesion except the inefficient right auricle. As is shown clinically and experimentally, the left ventricle cannot overcome the deficiency as the right does in mitral lesions; in animals, after artificial damage to the tricuspid valves, the left ventricle is normal or a little atrophied. Franke cites cases to show that a certain degree of compensation does occur, that patients with serious tricuspid lesions may live comfortably for considerable periods of time, and that even after compensation has been broken, it may be satisfactorily re-established. He considers three factors as important in maintaining it. Hypertrophy of the right ventricle keeps up pressure in the pulmonary circulation and this pressure may be above normal, as is evidenced by the much accentuated second pulmonic sound. During diastole it exerts a suction action which assists the flow of blood from the auricle and veins. The elasticity and passive resistance of the auricle and large venous radicals prevent, to a certain degree, regurgitation. The contractile force of the hypertrophied right auricle, Franke thinks, is of small moment, as the presystolic wave formed in venous pulse tracings by its contraction is scarcely visible and certainly not accentuated above the normal. A very important feature, however, and a rather ingenious assumption is the position he gives the peripheral vessels in maintaining compensation. Hasebrock has drawn attention to what he terms the systole and the diastole of the peripheral vessels, and has pointed out its importance in sustaining the general circulation. Franke likens this action, which he thinks is accentuated by the passive congestion of tricuspid insufficiency, to the role the right ventricle plays in mitral lesions. This contractile power in the peripheral vessels, he believes, is most evident in the liver. The systolic regurgitant wave beating back into the veins finds its freest path along the hepatic vein, which is without valves. The greatest damming back, then, must occur in the liver, which is the meeting point of two venous waves coming in opposite directions; one the hepatic, the other the portal system. The pressure in the portal vein measures only from 7 to 13 mm. of mercury, while that in the hepatic, with an actively working hypertrophied right ventricle,

must be decidedly higher. It is difficult to understand the absence of ascites in such cases unless there is some manner of regulation, and Franke ascribes such a self-regulation of the blood-flow to the liver itself. He assumes that, during the cardiac systole which is the diastole of the liver, blood is sucked in from the portal vein to be thrown with renewed force into the inferior vena cava by the succeeding contraction of the liver vessels and from here drawn into the right ventricle by its suction action.

The Intestinal Origin of Pulmonary Anthracosis.—SCHULTZE (*Münch. med. Woch.*, 1906, liii, 1702). The object of this article is to refute the conclusion of Calmette's students. This French school is accumulating more and more evidence in support of the intestinal origin of pulmonary tuberculosis, and recently van Steenberghe and Grysez have revived, from an experimental standpoint, Villoret's view of the intestinal origin of anthracosis. In their experiments on guinea-pigs and rabbits they mixed coal-dust and particles of India ink with the food, which, in some instances, they allowed the animals to eat, in others introduced directly into the stomach by means of a tube. At autopsy the pigment was found in the lungs and only in the lungs, the abdominal organs and mesenteric glands being free. The same result was obtained by intraperitoneal injections. In from twenty-four to forty-eight hours after an intraperitoneal injection of India ink they were able to demonstrate an anthracosis of the lungs and the tracheobronchial glands, while all other organs showed no pigmentation. Schultze, in repeating these experiments, comes to different results. After the intraperitoneal injections he finds a pigmentation of the lungs, but these are neither the only organs affected nor do they show any special predisposition toward its accumulation, for there is more pigment in the spleen and the liver than in the lungs. In his feeding experiments he obtained the same results as van Steenberghe and Grysez, the pigment being recovered only in the lungs, but his interpretation is different. He feels convinced that in feeding experiments, even when undertaken with the aid of a tube, it is impossible to exclude inhalation, and, indeed, this is how he explains its deposit in the lungs in these experiments. The fact that it is found only there, he believes, is almost convincing evidence as the distribution is so different when it is spread by the blood-stream. In a rabbit with a gastrostomy fistula he introduced pigments into the stomach over a period of two months and at section was able to find no deposit in the lungs.

Estimation of the Functional Capacity of the Heart.—FRITZ LEVY (*Ztschr. f. klin. Med.*, 1906, lx, 64). Ketzenstein has shown experimentally that when a large section of the arterial tree is suddenly cut off there is a rise of blood-pressure, and he has applied this principle to the functional study of the heart in man. The method is to determine the pulse-rate and the systolic blood-pressure in the brachial arteries and then compress by digital pressure the femoral arteries. Normally, a rise of blood-pressure of from 5 to 15 mm. of mercury occurs, while the pulse-rate remains constant or falls a little. Under certain conditions this rise is absent or there may even be a fall in the pressure associated with an increase in pulse-rate, a condition which Ketzenstein interprets as evidence of cardiac insufficiency. In cases of marked hypertrophy the

rise is considerably more than 15 mm. Levy has applied this method extensively and details his results. In most normal hearts he finds a rise of pressure does follow femoral compression, the rise rapidly subsiding when pressure is removed. The patients showing no rise were nervous, easily excited women in whom the method cannot be employed. Well-compensated valvular lesions display the normal rise, as do also neurasthenics with subjective heart symptoms. In cases of marked hypertrophy a rise of 15 mm. is the minimum to be considered normal. Anything less than this is classed as an insufficiency, and Levy quotes cases to illustrate the point. In wasting diseases and acute infections a fall, instead of a rise, is frequently observed and is held to indicate a serious loss of power in the heart. A similar fall was observed in some cases of valvular heart lesion, and the course of the disease confirmed the bad prognosis indicated by the method. The results in convalescence from acute infectious diseases are ranked as of a high order of importance and seem to furnish some idea of the condition of the heart. A convalescent typhoid patient, in spite of a drop of 10 mm. of mercury and a rise in rate of from 8 to 10 beats, was allowed out of bed because he felt so well, but was immediately taken with severe prostration. A patient with scarlet fever had a similar attack after leaving bed while the blood-pressure reaction was a falling one. As improvement occurs the rise after compression becomes steadily greater and greater. A case of mitral insufficiency showed a similar steady inclination to rise during recovery from broken compensation. Levy thinks that one of the greatest values of the method is in following injury done the heart by an acute infectious disease and in enabling us to gauge the length of time necessary to spare the heart any overexertion.

The Effects of Severe Muscular Exertion on the Circulatory Apparatus, the Kidneys, and the Nervous System.—BALDES, HEICHELHEIM, and METZGER (*Münch. med. Woch.*, 1906, liii, 1863) have made examinations of the participants in a 100 kilometer walking race before and after the contest. Those engaged in the race were young men between the age of seventeen and twenty-seven years. Of the twelve examined, all were normal except one whose urine contained a trace of albumin without formed elements in the sediment. Immediately upon finishing, the urine of all showed albumin varying in amount from a slight trace to 0.5 gram per liter by Esbach's method. In four cases the presence of blood was determined by chemical reaction. The specific gravity of all cases was very high. Casts and epithelial cells were found in nine cases and red blood corpuscles in the four whose urine showed the presence of blood chemically. By percussion the heart outlines in all cases were so appreciably increased that the authors, taking into account the possibility of error by this method, are still convinced that there must have been an acute dilatation. There was a much lower blood-pressure reading after than before the race. The pulse-rate was much increased, but by palpation no special changes in quality could be discovered. There was an average loss of four pounds in weight during the contest. The general condition of the contestants was good. There was no unusual dyspnœa, no palpitation, no cyanosis. In one there occurred a short fainting attack. Several days after the contest the authors were able to examine three of the participants, and the abnormal conditions noted immediately after the race had completely disappeared.

SURGERY.

UNDER THE CHARGE OF

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Concerning Reported Recurrences after Prostatectomy for Simple Hypertrophy.—ANDRE (*Annales des Maladies des Organes Genito-Urinaires*, July 1, 1906) says that he formerly believed with others that such recurrences could occur, but that now he does not think this occurs after the surgeon has removed the enlarged prostate as completely as possible by the recent methods. He refers to a case in which, at first, he believed that reproduction of prostatic tissue took place, but the later evolution of the affection showed that cancer was present. Without doubt a partial prostatectomy can be followed by a true recurrence, but when a complete operation is so followed, it is probable that a cancerous prostate and not a simple hypertrophy was present. The diagnosis between the two conditions is often difficult. During the operation on a second case he was able to recognize the presence of cancer.

The Surgical Treatment of Subclavian Aneurysms.—SAVARIAUD (*Revue de Chirurgie*, July 10, 1906) states that aneurysms of the subclavian artery should be divided into two groups those external to the scalenus, and those which are external and internal to the scalenus. The first group is essentially surgical. They may be treated by extirpation, or by ligature, which should be placed as far as possible in advance of the aneurysm. The combination of the two methods may be employed, the Anel ligation to be followed by the extirpation if this seems possible. For the second group the ligature of Anel is too dangerous, while the Brasdor or distal ligature gives a mortality almost nil, and the later results frequently are remarkable.

Gastrocutaneous Fistulæ, Consecutive to Gastric Ulcer.—PATEL and LARICHE (*Revue de Chirurgie*, July 10, 1906) say that this condition is relatively rare. It results from a perigastric focus of suppuration opening on the external surface, spontaneously or from an incision. It may result without the formation of an abscess that is clinically appreciable. It is then due to a gradual invasion from mild infections. The point of election is the upper part of the stomach, which is least movable and can the more easily adhere to the abdominal wall. Once established their characteristics vary according to their location. If they are high near the heart, the discharge is intermittent; if low near the pylorus, the discharge is constant. In the former a good general condition is maintained for a long time; in the latter, on the contrary, it

rapidly becomes bad. In the former medical treatment may be tried, the edges of the wound being left to cleanse themselves, and operation being done only if a cure does not result. The direct methods of operation, by excision of the ulcer and suturing the opening in the stomach, are to be preferred to the indirect method of gastroenterostomy. In the case of a fistula situated low, one should attempt its closure at once. The best method is to close the fistula by direct suture, although this is not always followed by success.

Pain in the Bladder in Women.—ROCHET (*Annales des Maladies des Organes Genito-Urinaires*, July 15, 1906) calls attention to frequent attacks of pain in the bladder, rebellious to treatment, which cannot easily be attributed to the ordinary causes of cystitis, as gonorrhea, tuberculosis, etc. In the great majority of cases the urine is disturbed and the bladder infected. In certain cases, however, the urine though examined with care, does not show apparent trouble and is almost clear. In general, blood is rarely observed in the urine. Upon vaginal examination and the passage of a urethral instrument, pain is not experienced until the neck of the bladder is reached. A careful examination of the bladder, the kidney, and the urine will sometimes be necessary to eliminate a beginning tuberculous cystitis. Tabes must sometimes be eliminated also. The pain may be due to gonorrhœal or puerperal infections, of long standing, which have been overlooked.

The Open-wound Treatment of Skin Grafting.—GOLDMANN (*Zentralb. f. Chirurgie*, July 21, 1906) says that he has had excellent results with the open-wound treatment of skin grafted fresh and granulated surfaces. Organic fixation of the transplanted flap, as has been frequently shown, occurs after twelve to twenty-four hours by means of the abundant newly formed fibroblasts and capillaries. Previous to this it is more or less mechanical from the plasma. The chief object should be to secure this fixation during the first hours, and for this purpose, the open-wound treatment will be most effective by drying the cementing substance. According to Goldmann's experience, after the grafts have once taken hold, the kind of dressing is not important. Either a moist or oily dressing may be employed to dissolve the crusts or scabs, so that the grafts may not be injured. The essential advantage of Weischer's method is not due to the periodical irrigation with salt solution to prevent coagulation of the secretion at the edges of the grafts, but to the accumulation of a cementing substance from the removal of the superficial granulations. Goldmann says that the vesical formation does not occur between the granulating surface and the grafts, but between the stratum Malpighi and the mucosum of the epidermis, and is an expression of the defective nourishment of the skin. As soon as the grafts are sufficiently nourished it disappears.

Exposure of the Heart in Wounds of this Organ.—WILMS (*Zentralb. f. Chirurgie*, July 28, 1906) says that the flaps ordinarily employed are suitable for the suturing of wounds of the anterior surface of the heart, but make a suture of the posterior surface difficult. In operating on a case with an anterior wound of entrance and a posterior wound of exit he found it necessary to resect the sternum before he could suture the posterior wound. He thinks that a long intercostal incision, as employed by Mikulicz and Sauerbruch, would, after opening the

pericardium, give a free exposure for attacking the posterior surface of the heart. It should be placed in the fourth or fifth interspace, according to the situation of the wound. Division of the fourth or fifth rib would add much to the extent of the exposure. Moreover, the duration of the operation would be considerably shortened.

A Contribution to the Study of Cancer of the Rectum.—MARTIN DU PAN (*Revue de Chirurgie*, August 10, 1906) concludes that sedentary occupations, habitual constipation, hemorrhoids, and traumatisms have not the importance generally accorded them in the etiology of cancer of the rectum. Its development is much more rapid before forty years of age than in advanced age. Its insidious origin is one of the principal obstacles to the improvement of the final results from operation. Early diagnosis is rare. It will be more common, and the operative treatment more beneficial, when physicians generally follow the practice of digital examination of the rectum in all troubles of defecation. In the author's statistics the average duration of life in most patients not operated on is twelve months; in those subjected to radical operation it is fifty-six months. The height of the cancer, the presence of indurated glands, adhesions to the prostate or vagina are not contraindications to extirpation of the rectum. Immobility alone is an absolute contraindication. A preliminary colostomy should be avoided if possible, and should be employed only in cases of ileus so grave as to put the life of the patient in immediate danger. The coccygeal operation of Kocher consists of a posterior incision in the median line, with resection of the coccyx. It is the method of choice for the removal of tumors of the ampulla and superior part of the rectum. The best treatment of the upper cut end of the intestine is to fix it at the anus, with or without invagination in the inferior end deprived of its mucus membrane. The circular suture of the two cut ends should be abandoned, because of the great danger of infection. The peritoneum, however, should be sutured as exactly as possible, after fixation of the intestine, and drainage should be avoided. When infection appears the wound should be opened at once and irrigated. The author's mortality was 14.58 per cent., and was favored by the use of ether instead of chloroform. Local recurrences operated on survived in 39.7 per cent. of the cases. Careful watching of the patient after operation is, therefore, important to detect recurrences, as they rapidly become inoperable. Immediate hemostasis, as complete as possible, and the avoidance of denuding the neighboring bone, are important, in order to avoid vascular metastases and cancerous adhesion to the bone.

Wound of Thoracic Duct; Ligature; Recovery.—FULLERTON (*Brit, Med. Jour.*, June 16, 1906) says that during the removal of tuberculous glands on the left side of the neck the thoracic duct was ruptured. On sponging away the escaping opalescent fluid the open mouth of the ruptured duct was seen and immediately caught with an artery clip. The duct on the proximal side of the ligature immediately became distended and seemed ready to burst. The distal end was found but did not allow the escape of fluid. It opened by three smaller vessels into the internal jugular vein. It was ligated, the wound closed with drainage, and during the latter dressings no fluid escaped. The patient recovered.

From a study of the recorded cases the dangers would appear to be: (1) Entrance of air into the veins; (2) rupture of the distended duct on the proximal side of the ligature; (3) inanition from draining away of the chyle; (4) possible dissemination of tubercle from entrance of the organisms into the torn duct. The treatment consists in occlusion of the torn duct by ligature, clamps, or packing, and keeping the patient quiet on a low diet to limit the pressure in the obstructed duct.

Concerning Ligation of the Renal Artery and Vein.—JUNGANO (*Annales des Maladies Organes Genito-Urinaires*, June 15, 1906) says that from the result of experiments on three rabbits and two dogs, he concludes that complete arrest of the circulation in the renal artery and vein so interferes with the nutrition and function of the kidney that a nephrectomy should be done. The collateral circulation is not sufficient. The renal epithelium undergoes necrosis and is replaced by cicatricial tissue, the necrosed material being absorbed and producing a toxic effect on the organism. This noxious effect is increased when the organism is in a condition of lessened resistance, as from a lesion of the renal vessels, from the hemorrhage which ensues. Besides, the injuring instrument may introduce infection, which in the area of degeneration finds a propitious field for development.

Etiology and Treatment of Oblique Inguinal Hernia.—MURRAY (*Brit. Med. Jour.*, June 16, 1906) concludes that the main factor in the causation of the hernia is the presence of a preformed sac and a patent funicular process. Whether the bowel will or will not enter this funicular process depends, primarily, on the size of the opening at the internal ring; and secondarily, on the strength of the muscles guarding it. The only satisfactory treatment is by operation, and the earlier the better. The essential point is to obliterate so completely the sac as to render the peritoneal surface free from any dimpling or depression. The divided aponeurosis of the external oblique should be subsequently united by overlapping, for the inguinal canal is thus narrowed, lengthened, and its original obliquity restored.

The Treatment of Cancer of the Stomach.—ROBSON (*Lancet*, August 18, 1906) says that there were 19,607 deaths from cancer of the stomach in England and Wales during the years 1901-4. 5 per cent. ran their course without local signs. Exploratory incision is the only reliable diagnostic resource in a considerable proportion of the cases. He advised that it should be done in a suspected case, if repeated examinations of test meals show diminished digestion and a diminution of free hydrochloric acid and the presence of lactic acid. In 59.3 per cent. of gastroenterostomies for later cancer, the long history of painful dyspepsia suggested the possibility of ulcer preceding the malignant disease. This is an additional incentive to the earlier surgical treatment of rebellious ulcers. Inflammatory masses about an old ulcer may so continue to obstruct the pylorus as to cause death. A gastroenterostomy sometimes causes a cure. Gastrostomy and jejunostomy for irremovable growth at the cardiac end of the stomach, in a fair proportion of cases, leads to great prolongation of life, while in thirty cases operated on by Robson there was only 5 per cent. mortality.

The good results from gastroenterostomy in irremovable pyloric

growths are well established, and the presence of a manifest tumor does not mean that it is too late to perform a radical operation. The disease may involve a great part of all of the stomach, so that it is irremovable, and gastrectomy is impracticable. Robson has performed jejunostomy with advantage in two such cases. The patients were relieved of pain; one lived three months and the other twelve months. The immediate risks of partial gastrectomy as calculated from a considerable series of cases are between 14 and 16 per cent. Of twenty-seven cases of total gastrectomy, collected from all sources by Peterson, ten patients died, a mortality of 30 per cent.

The thorough removal of the disease may bring about as much relief to the patient as does the operation for the removal of cancer of the breast, uterus and other organs of the body, and in some cases a complete cure may follow.

Successful Treatment of a Case of Thoracic Aneurysm, Threatening to Rupture Externally.—YOUNG (*Lancet*, September 22, 1906) reports a very interesting cure by what was practically the Tufnell treatment. It consisted of as nearly absolute rest as possible, restricted diet for a week and later an ordinary fish diet, no stimulation, and potassium iodide, grains 10 three times a day. The dose was quickly and steadily increased so that by the end of the third week 60 grains was being taken three times a day, with no ill effects at any time. As a local application to the swelling, collodion was painted all over the surface, every night and morning. Instead of continuing his previous downward progress, he commenced to improve from almost the commencement of the treatment. At the end of three weeks the patient said he had not been so well for four years. In about six weeks he was discharged apparently cured.

THERAPEUTICS.

UNDER THE CHARGE OF

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Calomel in Enteric Fever.—C. B. KER (*Edin. Med. Jour.*, 1906, No. 1, p. 29), after discussing the use of various antiseptics in typhoid fever, lauds calomel as being superior to them all, particularly when employed in connection with intestinal irrigations. He denominates his treatment "antisepsis by elimination," and has used it in 758 cases of enteric fever. The treatment consists in administering aperient doses of calomel (3 grains) every second or third day, supplemented by hot water

irrigations of the colon. The diet is chiefly milk, and water-drinking is encouraged. The advantages of the method are that it produces no pain and does not cause diarrhœa. The percentage of perforations was under 2 per cent., a rather low figure; hemorrhage occurred in 8.04 per cent., which seems large, but the loss of blood in many of the instances was slight. Marked meteorism is a contraindication to the use of calomel, but this manifestation may be caused to disappear by giving a small irrigation, and calomel may be allowed after twenty-four hours, unless blood appears as the result of the enema. Mercurialism was never noted. The death-rate of the patients treated as above was 9.36 per cent., but in calculating these figures no deductions are made of cases dying within forty-eight hours after admission. The author concludes with the statements that the calomel treatment is not unsafe, and ulcerative accidents are not increased. He makes the claim that the treatment leaves the patient free to deal with the enteric poison and relieves him from septic absorption; the bowel is kept clean, meteorism is reduced, and diuresis is assisted. The suggestion is made that this method in connection with the use of a specific serum, when such is obtainable, would be the most rational to employ in enteric fever.

Leukocytogenous Serum in Surgical Infections.—Paul Delbet (*Revue de Thérapeutique*, 1906, No. 11, p. 384) has employed the horse serum of Petit with considerable success in various surgical infections. The serum may be used either in fluid form or as a powder; it is applied locally to the lesion itself, or in its immediate neighborhood. It may be injected into the tissues or applied as a wet dressing upon gauze. The action of the serum is both local and general; under its employment the toxic symptoms become less marked, the temperature falls, and the pulse-rate diminishes. Locally, after from four to six hours, the wound becomes more moist and in the severe instances the pus becomes more abundant. No untoward symptoms have been noted. In puerperal infection the author packs the uterus with sterile gauze impregnated with the serum, and in the case cited rapid amelioration followed the procedure. Previous to the packing the septic contents of the uterus was removed by curettage. In four instances of appendicitis of severe grade success followed the use of the serum. In a case of postoperative peritonitis and in an instance of sloughing hemorrhoids the treatment failed.

The Effect of Potassium Iodide in Experimental Arteriosclerosis Due to Adrenalin Inoculations.—W. T. Cummins and P. S. Stout (*University of Pennsylvania Medical Bulletin*, 1906, No. 5, p. 101) after observing a series of experiments in rabbits state tentatively as a preliminary report that potassium iodide may be effectual in preventing the development of arteriosclerosis due to adrenalin inoculations. It seems probable that the salt has no absorptive properties, after the arteriosclerosis has appeared. Further research is being carried on by the authors.

The Treatment of Aneurysm by Relaxation of Arterial Tension.—H. Huchard (*Journal des praticiens*, 1906, No. 20, p. 307)) reports three instances of aneurysm which he has followed, two for eight years and one for four years, in two of which permanent cure has resulted from

treatment calculated to reduce vascular tension below the normal. The treatment consists in keeping the patient at rest in bed and in prescribing a diet from which soups containing an excess of fat, meats, especially those cooked rare, game, fish, cheese, salted foods, tea, coffee, spirits, heavy beers, and an excess of wine are eliminated. Tobacco is also forbidden. Drugs, such as trinitrine, tetranitrol, and sodium nitrite, were administered. The author considers that the iodides have been overrated in this connection. In syphilitic aneurysms mercurial injections are dangerous on account of their liability to affect the kidneys and, as a consequence, to cause increased arterial tension. The milk diet in connection with theobromine, which assists in eliminating vasoconstrictor poisons, is very helpful in reducing vascular tension.

Antithyreoidin in Exophthalmic Goitre and Kindred Affections.—H. L. ELSNER and J. R. WISEMAN,(*New York State Journal of Medicine*, 1906, No. 6, p. 235) state that they consider that antithyreoidin is a remedy which is effectual for the control of the annoying symptoms of typical and atypical cases of exophthalmic goitre. The greatest improvement is found in the relief of the tachycardia, precordial distress, and tremor. This improvement is hastened by rest in bed and diet regulation. These latter without the administration of antithyreoidin are much less effective. Improvement in one or more symptoms is likely to follow in from three to seven days after the beginning of treatment, but if no amelioration appears after three or four weeks the chances are against the occurrence of relief. The treatment should be continued for from four to eight weeks at a time, at intervals of two or three months, after subjective symptoms have disappeared. Patients without marked goitre, with slight exophthalmos, and the von Graefe symptom have been most benefited. The exophthalmos is the most rebellious of the symptoms. Nervous symptoms usually yield as the heart becomes slower. Most of the patients treated increased in weight, and when the antithyreoidin is stopped feel the lack of it greatly. The treatment produces no ill effects and cardiac dilatation and hypertrophy do not contraindicate its employment. The serum is administered night and morning in doses of from 15 to 30 minims, but in mild instances of the disease the initial dose is from 10 to 15 minims. It may be given in water, raspberry syrup, elixir of orange-peel, or a mild wine. If no benefit accrues from the above doses these may be increased to from 40 to 60 minims. Experience argues against permanence of cure in chronic cases.

Hypodermic Administration of Iron and Arsenic in the Anemia of Pretuberculous Conditions.—B. R. SHURLY (*Jour. Amer. Med. Assoc.*, 1906, No. 24, p. 1833) believes that hypodermic medication with iron and arsenic, together with strychnine and the hypophosphites, offers a prompt and powerful reconstructive adjunct to the pure air, good food, and sensible hygiene that are essentials in pretuberculous conditions. The green ammoniated iron citrate can be introduced into the system without danger in doses of from ¾ to 1½ grains, while sodium arsenate is given in doses of from 1/60 to 1/30 of a grain. The injections of solutions of these drugs are given deeply into the muscles of the buttocks or back. Only slight pain attends the procedure and a general feeling of well-

being follows the treatment. A full dose of the iron within five minutes causes a feeling of tension in the head, tingling sensations, and a flushing of the face. Doses larger than 1½ grains may cause nausea or vomiting. The hypodermic method of administration obviates injury to the stomach or teeth and does not cause gastric disturbance or constipation. The treatment is contraindicated in fever or acute hemorrhage. Daily injections should be followed by a 5 to 10 per cent. increase in the hemoglobin at the end of the first week.

Nitrogen Injections in Tuberculosis.—L. BRAUER (*Deut. med. Woch.*, 1906, No. 17, p. 652) reports an instance of tuberculosis which was characterized by hectic temperature and extensive lesions, and in which nitrogen was injected upon four occasions, in quantity about three pints at a time. After the first injection the fever disappeared for about three weeks and after the subsequent injections similar results were noted, but they were less lasting. The collapse of the lung caused neither dyspnœa nor cyanosis and the patient's general condition exhibited improvement. The technique of the injection was as follows: The site chosen was in the seventh intercostal space between the posterior axillary and the scapular lines at a point where the pleura seemed to be normal and the lung little affected. Under local anesthesia an incision about an inch long was made down to the parietal pleura. The latter was punctured by a trocar and cannula, through which the gas was injected, having previously been passed through 1 to 1000 mercury bichloride solution. The wound was then sutured. The nitrogen is but slowly absorbed and the good effect of the treatment is produced by compressing the lung, lessening its congestion, and putting it at rest. The compression is evidenced by an increase in the expectoration following the procedure. It may be that a condition of venous stasis is established which acts upon the infectious process.

OBSTETRICS.

UNDER THE CHARGE OF

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Abdominal Section during Pregnancy for Carcinoma of the Ovary and for Ovarian Tumor with Twisted Pedicle.—SCHAUTA (*Zentralb. f. Gyn.*, No. 25, 1906) reports abdominal sections during pregnancy for ovarian tumor with twisted pedicle. The first case was that of a multipara, whose labors had been normal. At the fourth month of pregnancy she came under observation complaining of pain in the right lower portion of the abdomen. The pain suggested disease of the appendix. Under anesthesia a tumor the size of a fist could be found which was movable. Abdominal section was made with a right lateral incision, and a parovarian cyst with twisted pedicle was removed. The pregnancy went on undisturbed. The second patient was in the fourth

month of pregnancy when she was taken with severe pain in the right lower portion of the abdomen. This was thought to be appendicitis. The patient remained in bed eight days, when she was apparently better. Pregnancy proceeded and was terminated by labor. Four weeks after labor the patient was examined, and she was found to have a tumor the size of a fist, directed toward the left side of the abdomen. This tumor did not seem to be connected with the uterus. At operation an ovarian tumor was found adherent, and with a very long thin twisted pedicle. The appendix was adherent to the tumor and very little altered in its substance.

Schauta also reports a case of carcinoma of both ovaries complicating pregnancy. The patient was five and one-half months advanced, and complained of various indefinite pains in the abdomen, with fever and enlargement of the abdomen. This rapidly increased and on examination the uterus could scarcely be felt. On opening the abdomen a large quantity of ascitic fluid was removed, and five months' pregnancy was found present, and in addition a tumor of each ovary as large as a fist. These were found to be carcinoma with dissemination in the peritoneum of Douglas' cul-de-sac. The broad ligaments were removed as extensively as possible with the tumor. On the next day following operation the patient aborted.

Schauta also reports an interesting case of a woman who had had a tumor on the abdominal wall near the left flank, which was removed during the first month of a preceding pregnancy. From this she made a good recovery. In the seventh month of her fourth pregnancy a tumor appeared in the scar of the former operation. Through friction with the clothing, bleeding occurred from the tumor. Upon examination it was found to be as large as a child's head and involving only the abdominal covering. At operation the tissues were extensively removed, when the tumor was found attached to the fascia and attacking the peritoneum at only one point. It was a fibrosarcoma. The wound healed by granulation, as so much tissue was removed that the edges could not be brought together.

The Prevention of Difficult Labor.—HERMAN (*British Medical Journal*, June 30, 1906) contributes a paper upon this subject in which he calls attention to fatalities in labor following septic infection and disproportion in size between mother and child. Death from malpresentation and hemorrhage are largely avoidable. Death from eclampsia or rupture of the uterus in easy labor, or from acute yellow atrophy of the liver, cannot be foreseen and cannot be prevented. Accidents from disproportion between mother and child may be anticipated by measuring the mother's pelvis, and also by subjecting her to vaginal examination in order that tumors of the pelvis may be detected. Herman would not empty the uterus in cases in which the pelvis is so small that a living child cannot be born, but would let the mother go to term and perform, if necessary, Cesarean section. Pregnant patients should be examined after the seventh month, and if a malpresentation be found, attempts should be made to remedy it. When the back is posterior, the child can usually be turned by manipulation. If the child is obliquely, the head can usually be brought over the pelvic brim. In breech presentation it is often difficult to turn the fœtus about. Premature labor is advised in cases of moderate disproportion, the method being the use

of a bougie, followed if necessary by dilatation of the cervix with solid dilators and the introduction of De Ribe's bag. When the pains are weak and inefficient they should be helped by the careful use of forceps. For a patient who has become exhausted from obstructed labor craniotomy is the proper treatment and not Cesarean section; the latter should be done early and not upon an exhausted patient. Hemorrhage from separation of the placenta, if threatening, Herman believes should be treated by Cesarean section. In placenta prævia the use of the dilating bag is recommended. Postpartum hemorrhage is usually caused by exhaustion, and especially by using forceps, without regard to contractions of the uterus. Efforts at delivery should always be made while the uterus is contracting. If the uterus is imperfectly emptied, postpartum hemorrhage may also be expected.

Pemphigus of the Newborn.—KOBLANCK (*Zeit. f. Geb. u. Gyn.*, 1906, Band lvii, H. 3) reports a case of congenital pemphigus, the mother a multipara, who had during pregnancy a moderate catarrh of the bladder and vulva. Labor began with discharge of amniotic liquid, and sixteen hours afterward a puny child was born. No vaginal examination was made during labor. Immediately after birth on the skin of the buttocks and upper arm were found pemphigus vesicles. The palms of the hands and the soles of the feet were free. Gradually bluish-red blotches appeared on the face and cranium. Syphilis could be excluded and the case was considered one of intrauterine infection originating in the external genital organs. The vesicles healed in a few days and mother and child remained in good condition. To determine the cause of the infection Koblanck examined the contents of the vesicles of fourteen children, and of two mothers who became infected in the mammary glands while nursing the children. One case gave no cultures whatever, probably because the vesicles were found in the stage of drying. In nine cases, one of which was maternal. Staphylococcus aureus only was found. In the remaining cases the germ found resembled Staphylococcus aureus. The infection probably occurs from mechanical pressure on the delicate skin of the child, but this may also happen in a grown person, as seen in cases in which the mother's breast becames infected by nursing the child. Experimental inoculation is usually made by incising the superficial layers of the skin.

A Fifth Case of Inversion of the Uterus Successfully Treated by Application of De Ribe's Bag Inflated with Air.—PINARD (*Annales de Gynecologie*, May, 1906) reports his fifth case of inversion of the uterus, successfully treated by De Ribe's bag. The patient was a multipara who had a normal pregnancy. Labor was terminated by an easy application of the forceps. The entire labor lasted twenty hours, the actual period of expulsion seven hours. Traction upon the os was made to deliver the placenta, when the uterus inverted. There was no hemorrhage, and the placenta, attached to the fundus, was readily removed together with some clots, but as the membranes were attached at the internal os, it was necessary to tear through the placenta to deliver the membranes completely. The uterus was readily reduced, the patient suffering very little shock. Four days afterward the uterus again became inverted after the patient had emptied the urinary bladder. Efforts at reduction by hand failed, whereupon De Ribe's bag

was introduced and inflated with air. Its pressure did not cause pain, and within the twenty-four hours following, the uterus returned to its normal position. As a rule, in using the bag in this manner it should not be allowed to remain longer than eight hours.

Cesarean Section for Threatened Rupture of the Uterus.—POTOCKI (*Annales de Gynecologie*, May, 1906) reports the case of a patient, a multipara at term, who had been in labor twelve hours without the engagement of the head. Mother and child were in good condition. The pelvis was symmetrically contracted, the anteroposterior diameter measuring 9.8 cm. The type of pelvis was rachitic. When dilatation was complete the membranes were ruptured, amniotic liquid was slightly discolored. The anterior parietal bone presented, but the head still remained immovable. Engagement failed, although means were taken to relieve the patient's suffering. Her pains, however, became so severe as to demand prompt relief. The distension of the lower uterine segment was found to be excessive and uterine rupture was threatened; it was accordingly determined to deliver the child by Cesarean section. On opening the abdomen and the uterus the tissues were engorged and infiltrated with serum, giving evidence of severe birth pressure. A well-developed male child was delivered; the uterus packed with sterile gauze, which was carried through the cervix into the vagina, and the womb was closed by three rows of catgut stitches. Mother and child made good recoveries. The child's head was above the average in size and very well ossified.

Gonorrhœa in the Puerperal Period.—MAYER (*Monatschr. f. Geb. u. Gyn.*, 1906, Band xxiii, Heft 6) reviews the literature of this subject, and concludes that puerperal gonorrhœa may be a dangerous disorder. It can cause high fever and severe general infection with chills. The general picture may be that of systemic septic infection of severe grade. We cannot definitely distinguish how much of this condition is caused by toxins and not by bacteria. In severe cases with high fever we must suppose that mixed infection with streptococci and staphylococci is present in addition to gonorrhœa. Great variations in temperature, alternating between high fever and periods free from fever, are more characteristic of gonorrhœal infection than of sepsis. The statement sometimes made that fever developing late in the puerperal period is characteristic of gonorrhœa cannot be maintained. As regards the effect upon the children, in six children born of a gonorrhœal mother, four would be feeble or deficient at birth, while the other two would have less than usual power of resistance.

Gangrene of the Puerperal Uterus.—SCHMIDLECHNER (*Archiv. f. Gyn.*, 1906, Band lxxviii, Heft 3) reports the case of a patient who had had four normal labors, and who, during the fifth pregnancy, had considerable hemorrhage followed by an offensive discharge. The patient was thought to have had an abortion and was brought to the hospital. On examination a mass of decomposed tissue was found in the cervix. On further examination the uterus was as large as a fist, somewhat sensitive and anteflexed, and its wall very thin. Great care was taken to avoid rupturing the uterus, and a portion of the mass in the cervix was removed for examination. It was found to consist of necrotic uterine tissue, fibrin, disorganized and unrecognizable

cells, blood pigment, and pus cells. The patient grew worse, although on examining the blood no pathological organisms of an infectious character could be found. She was thought to have chorio-epithelioma or gangrene of the uterus. Under anesthesia the uterus was removed through the vagina; the right ovary was also removed, and the stumps of the broad ligaments brought into the vaginal wound, and packing of iodoform gauze inserted. On examining the uterus its muscle was found to be a dirty grayish brown and highly disintegrated. In several places the uterine wall was almost perforated. On microscopic examination the tissues were found in a condition of cellular necrosis. The patient made a speedy and an uninterrupted recovery.

GYNECOLOGY.

UNDER THE CHARGE OF

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Dermoid Cysts of the Ovary.—SCHOTTLAENDER (*Archiv. f. Gynäkologie* 1906, Band lxxviii, Heft 1) found in the walls of these cysts numerous cavities lined, and often filled, with epitheloid and giant cells, which represent dilated lymphvessels due to the irritation caused by the invasion into them of sebaceous material from the skin. This cell proliferation may be so marked as to justify the diagnosis of lymphangioma or endothelioma. The fact that these spaces are lined with lutein membrane does not prove that dermoids are developed from the ovum. According to Schottlaender they are secondary cysts; whether they all develop in this way, or are due to fetal inclusion, is not yet certain.

The Physiology of Uterine Contraction.—KURDINOWSKI (*Archiv. f. Gynäkologie*, 1906, Band lxxviii, Heft 1) from experiments on rabbits finds that cold excites contraction more than heat. Cold water acts more promptly in cases of uterine hemorrhage and a less quantity is required; nor is an intrauterine injection required, since the mere contact of cold with the portio is enough to excite general contractions. Long-continued mechanical irritation, as by rubber bags, leads to atony of the uterine muscle. Weak stimuli are better, such as electricity.

Intestinal Fistulæ following Laparotomy.—OSTERLOH (*Zentralbl. f. Gynäkologie*, 1906, No. 34) reported ten cases of intestinal fistulæ following laparotomy, with eight recoveries. In every instance the fistula healed spontaneously. In the discussion of the paper Leopold reported three cases, two terminating fatally; Peters two cases, in which the fistula closed without operation. The latter thought that in these cases the prime factors in the causation of the fistula was a peculiarly soft condition of the intestinal wall in a given case, especially when it was adjacent to a purulent collection.

Abdominal Myomectomy.—Bonier (Thèse de Lyons; Abstract in *Zentralbl. f. Gynäkologie*, 1906, No. 34) thinks that the ideal operation is removal of the fibroid alone, whenever this is possible, the disadvantages of total hysterectomy being the premature menopause and atrophy of the vagina. The younger the patient the more conservative should be the operation, although it may involve greater risk and difficulty. Bonier's own mortality in myomectomy is 3.3 per cent. The ultimate results were satisfactory. The uterus generally undergoes atrophy and the climacteric is normally established. Recurrence of the fibroid is rare.

Tuberculosis of the Cervix Uteri.—Lannes-Dehore (Thèse de Lyons; Abstract in *Zentralbl. f. Gynäkologie*, 1906, No. 34) finds that tuberculous disease of the cervix is most common between the ages of twenty and thirty years, occurs equally in nulliparæ and in those who have borne children, and that the infection may be either primary or secondary. Leucorrhœa is always present, and often amenorrhœa, dysmenorrhœa, and metrorrhagia. Fever was noted in only one case observed by Lannes-Dehore. Clinically three varieties may be presented—the miliary, ulcerating, and proliferating. The treatment is surgical unless advanced tuberculosis is present in other organs.

Ovarian Tissue in Dermoid Cysts.—Gentili (*Archiv. f. Gynäkologie*, 1906, Band lxxvii, Heft 3) from an examination of twenty-three dermoids concludes that in many cases an ordinary ovarian cystoma is invaded by dermoid tissue, the common picture presented being the filling of the lymphvessels and spaces with fat, so that the tumor appears to be almost like a lipoma.

Premature Menopause.—Darcanve-Movroux (Thèse de Paris; Abstract in *Zentralbl. f. Gynäkologie*, 1906, No. 31) emphasizes the fact that premature menopause must be distinguished from amenorrhœa due to chronic or acute diseases. In some instances the early disappearance of the menses may be referred to reflex nervous influences, or to superinvolution of the uterus, but more often to imperfect development. Delayed puberty, scanty and irregular menstruation and sterility, without impairment of the general health, point to insufficiency of the ovarian functions.

Rupture of Pyosalpinx.—Lejars (*Zentralbl. f. Gynäkologie*, 1906, No. 35) calls attention to the rare occurrence of intraperitoneal rupture of pus tubes and the difference between the gradual ulceration of the wall of an old pyosalpinx and the acute perforation of a recent abscess. He reports two cases of the latter, treated successfully by operation. In neither was there any history of traumatism, but it was evident from an examination of the specimens that the perforation was due to an ulcerative process, as in gangrenous appendicitis.

Sclerosis of the Uterine Bloodvessels.—Wittek (*Monatschrift f. Geb. u. Gyn.*, 1906, Band xxiii, Heft 6) describes the histological appearances presented in four uteri removed on account of intractable hemorrhage. It was noted that the continued use of ergot only increased the menor-

rhagia. This was explained by the condition of the intima of the arteries which had undergone connective-tissue hypertrophy. The result of uterine contractions was simply to compress the veins and to cause venous congestion, while the arteries were not affected on account of the rigidity of their walls. In one case Wittek believed that the arteriosclerosis was due to vasomotor disturbances, in the other to senile changes. This factor in the causation of menorrhagia is more common than is generally supposed, nor is the arteriosclerosis necessarily of inflammatory origin. Since frequent childbearing is a predisposing cause, the presence of arteriosclerosis should be inferred in the case of multiparæ in whom no other obvious reasons for menorrhagia can be discovered.

OPHTHALMOLOGY.

UNDER THE CHARGE OF

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Permanency of the Results in the Operative Treatment of High Myopia.—PAUSE (*Zischr. f. Augenhk.*, 1906, No. 11) publishes a continuation of Pflüger's monograph, "Suppression du cristallin transparent," Paris, 1899, in an attempt to determine the permanency of the results in the patients operated on by Pflüger up to 1894; twenty-four of forty-six patients could be found for examination. With the exception of one patient in whom central vision was lost from extensive choroiditis, the visual acuity was increased twice and fourfold and in one patient fivefold. Improvement in the function of the retina is to be regarded as the cause of such increase in the acuity. Central recent and old choroidal changes are not to be regarded as contraindications; on the contrary, the operation tends rather to conservation of central vision (in two out of three cases observed). The increase in the anteroposterior axis is not inhibited entirely but only checked. All the patients were well pleased with the result; many claimed that their sight was worse in poor light. Fukala's method of operating has not thus far been surpassed by any other.

A Diagnostic Point in Sarcoma of the Choroid.—PURTCHER (*Centralb. f. prak. Augenhk.*, May, 1906) emphasizes the diagnostic value of a dark deposit on Descemet's membrane and the iris in sarcoma of the choroid; these deposits somewhat resemble an hyphema and are due to

migration of sarcomatous elements from the tumor into the anterior segment of the eyeball, especially into the anterior chamber. Such "coffee-ground" collections in the angle of the anterior chamber evidently predispose to the increased tension which so often accompanies intraocular growths.

Protection of the Eyes against Ultra-violet Rays.—Dor (*Revue generale d'Ophtal.*, October, 1905) calls attention to the well-known fact that the ultra-violet rays have an injurious effect upon the cornea, lens, and retina, in general—like that of snow blindness and strokes of lightning. The best protection against these chemically active rays is yellow glass, such as is used by photographers. Such glass should be employed in the first lenses given after cataract extraction. Fortunately, there are also certain kinds of smoked glass which, without being very dark, are quite impervious to the ultra-violet rays, as is easily proved by photography. Dor proposes the term "achemical" for such lenses.

Stilling's Theory of Myopia.—(*Ztschr. f. Augenhk.*, 1906, No. 1.) In view of the prevalent misunderstanding as to his real views, Stilling again gives a comprehensive exposition of his hypothesis as to the production of myopia. Myopia occurs, in so far as prolonged near work is its cause, from too great development of the length of the eye due to pressure of the external muscles. It is not to be supposed that the pressure of the muscles directly affects the change in the shape of the globe, but rather that the tendons under tension offer an obstacle to growth in directions at right angles to their planes. Inasmuch as this obstacle is least active in an anteroposterior direction the eyeball in its growth naturally follows this line of least resistance. All the muscles are active in coercing growth under their pressure, but the oblique muscles are the controlling factor because their action is variable, while that of the other muscles is constant.

Filaria Loa.—Vail (*Amer. Jour. Ophthal.*, December, 1905) reports the case of a wife of a physician who experienced painful sensation with redness of the right eye during her residence in Africa, in 1899. A worm-like movement was observed beneath the conjunctiva, which disappeared after two hours at the external canthus; two days later the same phenomena were noticed in the other eye. Subsequently similar vermicular movements took place beneath the skin of the upper lids. Her husband succeeded by incision in removing some of these small worms, which, moreover, appeared at numerous other parts of the body and could be in part removed. The worms manifested a special partiality for the lids and tissues near the eye. Several of these worms were later removed (the condition having continued unchanged for years) by the reporter, and recognized as Filaria loa.

Results of Removal of the Clear Crystalline in High Myopia.—De Font-Reault (*Annal. d'Oculist*, 1906, vol. cxxxv) analyzes the results given by various statistics with particular reference to cases which have been followed over five years. Myopes of 20 D. generally become emme-

tropic. Visual acuity for distance is most frequently increased, but the opposite for near. Progression of increase of the anteroposterior axis is generally greatly diminished in the non-operated as well as in the operated eye, due no doubt to the abolition of binocular vision. The operation appears to exert little influence upon the choroiditis present. Detachment of the retina is rather more frequent. The operation has sometimes caused glaucoma at a more or less distant epoch. He concludes that the operation should only be done in eyes having a myopia above 20 D. in subjects requiring an improvement in their distant vision, and that it should only be performed upon a single eye.

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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Studies on Spirillum Obermeieri and Related Organisms.—Novy and Knapp (*Jour. Infect. Dis.*, 1906, iii, 291) have made a very extensive study of an organism causing relapsing fever in man. They offer a numbor of convincing proofs that Spirillum obermeieri is a bacterium and not a protozoon. It is probably related quite closely biologically to Treponema pallidum or Spirocheta pallida, and is very similar to the organism causing tick fever of Africa and Bombay relapsing fever, which facts add great importance to the work. The blood at the beginning of one of the paroxysms seen in relapsing fever has very little germicidal power, ana the spirillum will live in it in vitro as long as forty days. The organism rapidly dies, however, in blood withdrawn toward the end of a paroxysm, and the authors think that the course of the recurring paroxysms depend on a rise and fall of the germicidal properties of the blood. Men, monkeys, white mice, and grats are subject to the infection, although paroxysms do not occur in the last-named animal. All attempts at cultivation of the organism have proved unsuccessful. Both active and passive immunity was produced, rats being especially used, and a passive immunity could be established by injections of hyperimmunized blood. This procedure caused the spirilla to disappear rapidly from the circulating blood. In the hyperimmunized blood, and in the blood of animals which were recovering or had recovered from the disease, there is a germicidal substance that is probably distinct from the immune bodies which also exist. Active and passive immunity last about one month. Hereditary immunity can also be obtained and is probably due to intrauterine infection. Hyperimmunized blood has a distinct preventive and curative action in rats, mice, and monkeys, thus establishing a solid

basis for the hope of prevention and cure of relapsing fever in man. This immunized blood also has a strong agglutinative property in vitro and in vivo. Agglutination occurs to a slight extent in the blood at the time of crisis in a paroxysm. The agglutinating property of the serum may be used in the serum-diagnosis of the disease, and also as a means of identifying the organism.

Novy and Knapp believe that there is probably a group of relapsing fevers, and that the disease seen in Bombay and the Tick fever of Africa are caused by organisms distinct from Spirillum obermeieri. They are inclined to believe that relapsing fever may be conveyed by insects, and this is the first evidence that insects may serve as a means of transmission of a bacterial infection. Up to the present time the proof that a disease was transmitted by insects was considered as strong evidence against bacterial infection. The authors believe it is not improbable that the cause of yellow fever may be an organism belonging to this group.

The Relation between the Duration of the Disease and the Age of the Intestinal Lesions in Typhoid Fever.—It is usually stated and generally believed that in typhoid fever the formation of the intestinal ulcers progresses coincidentally with the course of the disease, so that roughly the various stages in the development of the intestinal lesions correspond to definite periods of the attack of fever. Thus, the infiltration of the lymphatic apparatus marks the second week, necrosis occurs in the third week, the slough takes place in the fourth week, and after the fifth week there is clean ulceration. WENNAGEL (*Deut. Arch. f. klin. Med.*, 1906, lxxxvii, 551) finds that this is true only in about 50 per cent. of ninety cases of typhoid fever which he has studied in Strassburg. The difficulty of finding out the day of onset is always to be taken into consideration, but Wennagel decided that the most accurate method was to count from the day on which the patient noticed his first symptoms, such as headache, malaise, etc. Accordingly, it was found that the stage of infiltration of Peyer's plaques occurred not only in the second, but in the third, fourth, and fifth weeks; and the stage of slough formation, sloughing, and clean ulceration from the second to the seventh week. Infiltration was found oftenest, however, in the second week (42 per cent. of the cases). Wennagel concludes that in the early stages of the disease advanced lesions, such as slough formation, do not occur. Before the third week there are seldom clean ulcers. Further than this it is not possible to determine from the anatomical findings at autopsy with any degree of accuracy the duration of the disease. Typhoid fever should be considered a general infection in which intestinal lesions may appear.

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